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Synthesis of Dibenzocyclooctyne-Dicobalt Hexacarbonyl and Dibenzocycloheptyne-Dicobalt Hexacarbonyl Complexes by Intramolecular Nicholas Reactions: Synthesis of Isoschizandrin, Schizandrin A and Tenuifolin

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Synthesis of Dibenzocyclooctyne–$Co_2(CO)_6$ and Dibenzocycloheptyne–$Co_2(CO)_6$ Complexes by Intramolecular Nicholas Reactions: Synthesis of Isoschizandrin, Schizandrin A and Tenuifolin

by

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2013

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ABSTRACT

Biaryl propargyl acetate dicobalt hexacarbonyl complexes readily undergo Lewis acid mediated intramolecular Nicholas reactions to afford dibenzocycloheptyne complexes. This thesis describes the extension of this protocol towards studies of intramolecular Nicholas reactions with similar biaryl complexes to form dibenzocyclooctyne–$Co_2(CO)_6$ complexes. These investigations have been performed on several different derivatives of biaryl systems and have afforded fair to good yields of dibenzocyclooctyne–$Co_2(CO)_6$ complexes. One of the major factors governing the yield of intramolecular Nicholas reactions was found to be the amount of Lewis acid employed along with absence or presence of EtN^iPr_2. The studies conducted have also shown that in some cases, upon the cyclization there is restriction of the biaryl axial rotation due to the four ortho substituents, which constitutes formation of an axis of chirality. In addition, we have also exploited intramolecular Nicholas reactions of biaryl propargyl acetate dicobalt hexacarbonyl complexes towards the synthesis of tenuifolin.

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LIST OF ABBREVATIONS

°	degrees
α	alpha
AB	AB quartet
Ac	acetyl
n-Bu	*normal*-Butyl
BRSM	based on recovered starting material
t-Bu	*tertiary*-Butyl
BTMSA	bis(trimethylsilyl) acetylene
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
m-CPBA	*meta*-chloroperbenzoic acid
CSA	camphorsulfonic acid
Cy	cyclohexyl
d	doublet
dd	doublet of doublets
DBU	1,8-diazabicycloundec-7-ene
DCE	dichloroethane
DFT	density functional theory
DIBAL-H	diisobutylaluminium hydride

DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppm	1,1-bis(diphenylphosphino)methane
DTBP	2,6-di-*tert*-butylpyridine
E_g	geometrical strain energies
Et	ethyl
EtOAc	ethyl acetate
FVP	flash vacuum pyrolysis
GC-ToF	gas chromatography – time of flight
HRMS	high resolution mass spectrometry
IBX	2-iodoxybenzoic acid
IR	infrared spectroscopy
Me	methyl
m/e	mass/charge ratio
MHz	megahertz
min	minutes
mL	milliliters
mmol	millimole
mol	mole
NMO	4-methylmorpholine *N*-oxide

NMR	nuclear magnetic resonance
Nu	nucleophile
Ph	phenyl
PIFA	phenylinodine(III) bis(trifluoroacetate)
ppm	parts per million
^{i}Pr	isopropyl
PTSA	*para*-toluenesulfonic acid
q	quartet
RCM	ring closing metathesis
rt	room temperature
s	singlet
t	triplet
TBS	*tert*-butyldimethylsilyl
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl

CHAPTER 1 : INTRODUCTION

1.1 Angle strained cycloalkynes

The first attempts at synthesizing cyclic alkynes were conducted in the early twentieth century.[1,2] Isolability due to the low stability of cyclic alkynes presented the major challenges. Ring sizes of cycloalkynes play the most important roles in these properties.[3] For example, cyclononyne **(1)** and cyclooctyne **(2)** are isolable compounds, but cycloheptyne **(3)** and cyclohexyne **(4)** cannot be isolated and mainly exist as short-lived intermediates.

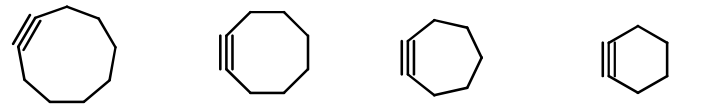

Figure 1.1. *Structures of cyclononyne, cyclooctyne, cycloheptyne, cyclohexyne.*

Cycloheptyne has a half-life of less than one minute in 0.016 M CH_2Cl_2 solution at -25 ^oC due to the great angle strain.[4] The derivative 3,3,6,6-tetramethyl-1-thia-4-cycloheptyne **(5)** was the first isolable seven-membered alkyne synthesized successfully, which was accomplished by subjecting the bis-hydrazone compound **(6)** to a reaction involving Ag_2O in THF (Figure 1.2).[5] The success of this synthesis was attributed to gem-dimethyl groups providing additional kinetic stability to the alkyne, and the presence of the longer C-S bonds reducing the angle strain of the triple bond. Compound **(5)** was stable even at elevated temperatures of up to 140 ^oC, however the reaction was sluggish and only produced a 6 % yield.

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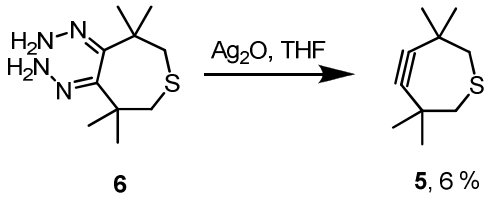

Figure 1.2. *Formation of 3,3,6,6-tetramethyl-1-thia-4-cycloheptyne..*

The gem-dimethyl stabilizing effect was utilized to synthesize and isolate 3,3,7,7-tetramethyl-cycloheptyne **(7)**. The $Pd(OAc)_4$ mediated elimination reaction of bis-hydrazone **(8)** produced the intended product cycloheptyne **(7)** in a 25 % yield (Figure 1.3).[4]

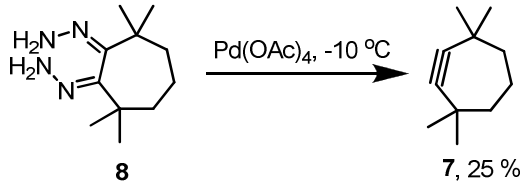

Figure 1.3. *Synthesis of 3,3,7,7-tetramethylcycloheptyne.*

Cycloheptyne **(7)** is less stable than its heterocyclic analog **(5)**. The half-life of **(7)** is approximately 1 day at 25 ^{o}C in a 0.2 M CCl_4 solution, and as a neat solution it dimerizes within 1 h. The presence of unstable cycloheptyne intermediates has also been proven by the formation and trapping of 4,5-didehydrotropone.[6] This compound has shown great reactivity in [2+2] cycloaddition reactions with several different 1-morpholino-1-cycloalkenes.[7] Cycloheptyne **(3)** and **(9)**, along with cyclohexyne **(10)**, have also been generated by argon-matrix photololysis from their corresponding cyclopropenones (Figure 1.4).[8] Due to their instability, these cycloalkynes were generated at approximately 15 K and immediately characterized by IR spectroscopy.

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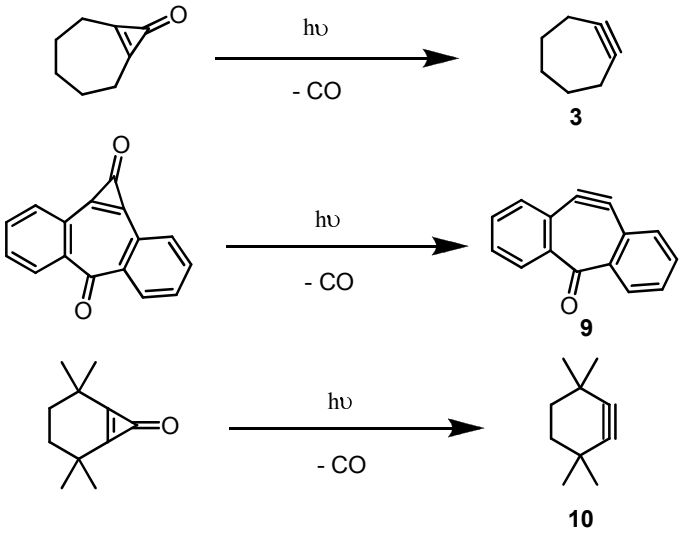

Figure 1.4. *Cycloalkyne preparation by argon-matrix photolysis.*

Benzynes are one of the most extensively studied cyclohexynes.[9,10] There are multiple ways to generate benzyne intermediates, and most include the addition of strong bases such as *n*-BuLi or amide bases or the use of elevated temperatures. As an example, aryl bromide **(11)** can be converted efficiently to benzyne intermediate **(12)** by the use of *t*-BuNHLi, where lithiated intermediate **(13)** is generated in the process and undergoes elimination to form benzyne **(12)** (Figure 1.5).[11] In similar fashion, selective ortho metallation and elimination of 1,2,4-trichlorobenzene **(14)** by $LiNH_2$ can be carried out to generate dichlorobenzyne intermediate **(15)**.[12] Heat promoted elimination reaction of benzene-diazonium-2-carboxylate **(16)** has been proven to generate benzyne **(17)**, which can be trapped by isoquinolinedione derivative to synthesize norcepharadione B (Figure 1.5).[13] However, due to the instability of benzynes, isolation has proved to be impossible. The solution to the instability is normally formation of benzyne complexes with early or late transition metals, as demonstrated later in the chapter.

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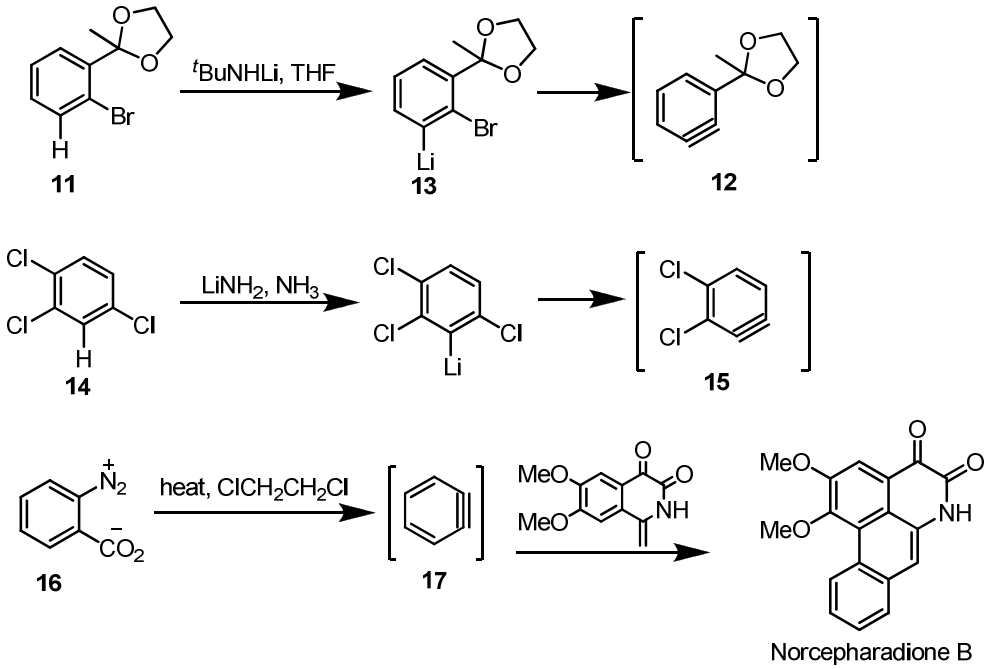

Figure 1.5. *Base and heat generated benzyne intermediates.*

The generation of cyclohexyne **(4)** and 3-azacyclohexyne **(18)** have been reported.[14] Subjecting isoxazolone **(19)** and **(20)** to flash vacuum pyrolysis (FVP) produces cyclopentylidene carbene as an intermediate which then undergoes rearrangement to form the corresponding cyclohexynes (**4)** and **(18)**, respectively (Figure 1.6). The products were matrix isolated at 77 K and characterized by IR spectroscopy. Cyclohexynes can also be generated efficiently from 1-cyclohexenyl-iodonium salts through the E2 and E1 elimination reactions by utilizing acetate or other bases.[15] The presence of unstable cyclohexynes can be determined by trapping the products with scavenger molecules.[16] Due to their high reactivity, cyclohexynes have been heavily used in natural product synthesis as reactive intermediates.[9,17,18]

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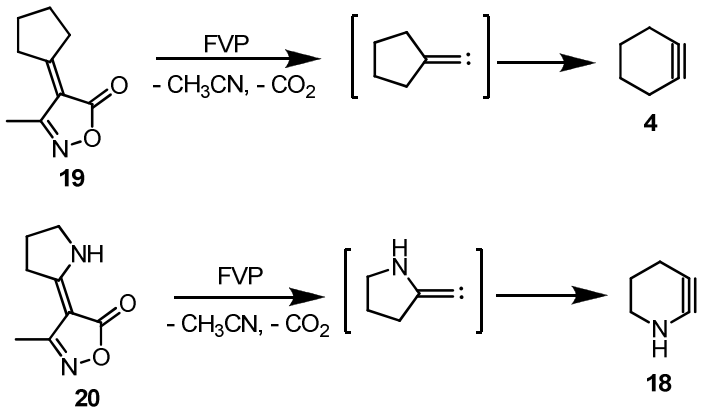

Figure 1.6. *Cyclohexyne and 3-azacyclohexyne synthesis by flash vacuum photolysis (FVP).*

Large numbers of cyclooctynes have been reported as stable molecules, which can be isolated in some but not all cases.[3,19] The generation of 2-cyclooctynone **(21)** was achieved by the reaction of 3-bromo-2-cyclooctenone **(22)** with K_2CO_3.[20] Highly strained 2-cyclooctynone **(21)** is a very reactive molecule and could not be isolated. In order to provide evidence that 2-cyclooctynone **(21)** was generated, trapping reagents including deuterated methanol, 1,3-diphenylisobenzofuran and cyclopentadiene were incorporated in the reaction media to generate 3-methoxy-2-cyclooctenone **(23)**, and the Diels-Alder products **(24)** and **(25)** respectively, in moderate to excellent yields (Figure 1.7).

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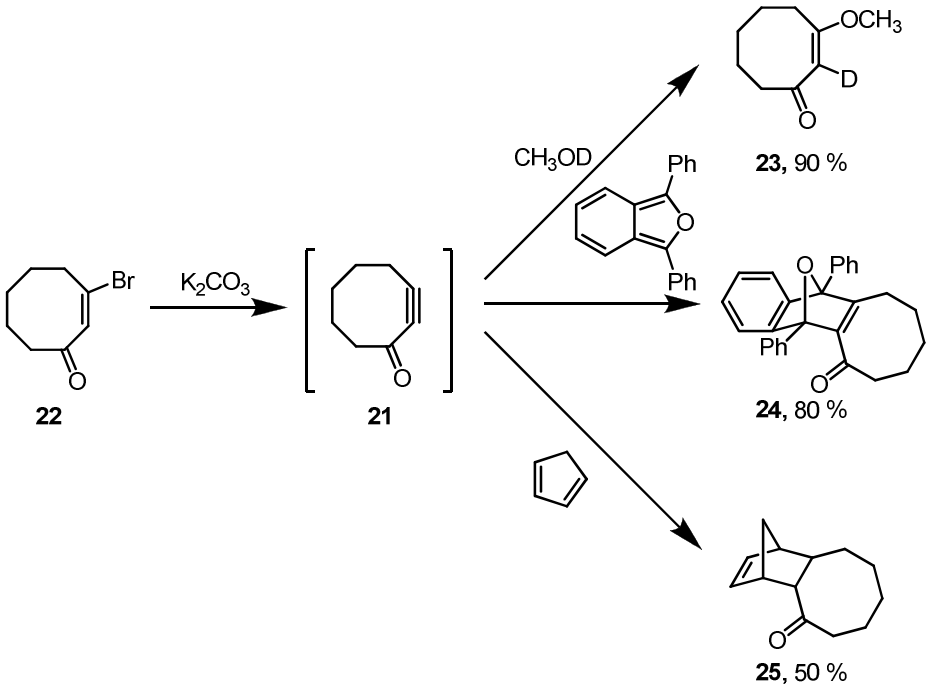

Figure 1.7. *Generation and trapping of 2-cyclooctynone.*

Small quantities of 1,5-cyclooctadiyne **(26)** had been previously prepared by polymerization of butatriene and have been shown to be stable at 0 ^{o}C under inert atmosphere.[21] Nevertheless, the first comprehensive study of the preparation and reactivity of 1,5-cyclooctadiyne **(26)** by cyclodimerization of butatriene was outlined by Wriz and co-workers.[22] Even though isolation of 1,5-cyclooctadiyne **(26)** by this method is possible, a maximum yield of 2 % by this method is not appealing. Accesses to 1,5-cyclooctadiyne **(26)** with improved yields can be achieved by the reaction of 1,5-dibromo-1,5-cyclooctadiene **(27)** with potassium *tert*-butoxide in the presence of 18-crown-6 (Figure 1.8).[23]

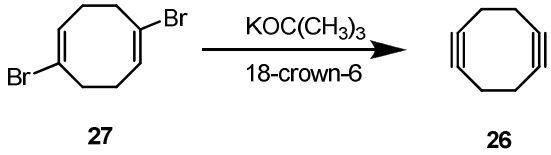

Figure 1.8. *Synthesis of 1,5-cyclooctadiyne from 1,5-dibromo-1,5-cyclooctadiene.*

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Cycloelimination reactions can be used to generate a variety of cyclooctynes.[19] Photochemical decarbonylation of cyclopropenone **(28)** produces the substituted dibenzocyclooctyne derivative **(29)** in yields ranging from 77 – 89 %, depending on the substituents at R_1 and R_2 (Figure 1.9).[24] DFT calculation at B3LYP 6-311G** level of theory for **(29)** have shown that the alkynyl carbons have a bond angle of 155 °. Cyclooctyne product **(29)** is a good candidate for the ring-opening alkyne metathesis reaction, since it was identified as stable under ambient conditions and exposure to light.

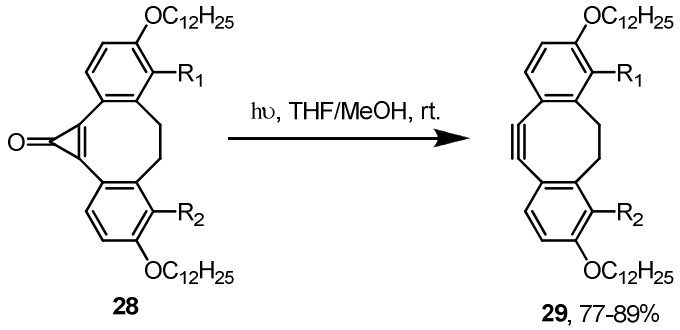

Figure 1.9. *Photochemical decarbonylation reaction in synthesis of cyclooctyne.*

Fragmentation of 1,2,3-selenadiazole **(30)** in a two step process has been successful in synthesizing cyclooctynol **(31)** (Figure 1.10).[25] This type of elimination reaction can be extended to include 1,2,3-thiadiazoles. In addition, the extrusion of nitrogen can be initiated by heating, irradiation, strong bases or certain metal salt complexes, which provides several different pathways for the cycloelimination reactions.[19]

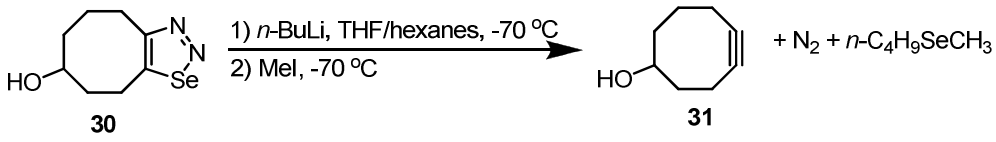

Figure 1.10. *Cycloelimination reaction in synthesis of cyclooctyne.*

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Geometrical strain energies (E_g) of cyclooctynes differ as the number of double bonds present in the ring changes (Figure 1.11).[26] The E_g value gradually increases upon the introduction of one, two or three double bonds in the system. Cyclooctyne, has an E_g value of approximately 50 kJ/mol, while cyclooctatrienyne is at the other extreme and has E_g value of approximately 140 kJ/mol. All of the cyclooctynes listed in figure 11 are isolable, with the exception of 1,3,5-cyclooctatrien-7-yne, it only exists as transient intermediate with half-life of 12 minutes in $5x10^{-2}$ molar solution at 25 ^{o}C.

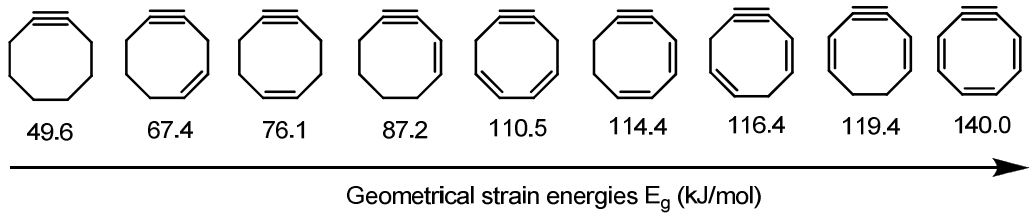

Figure 1.11. *Geometrical strain energies in cyclooctyne series.*

Due to their instability, cycloalkynes are often coordinated to mononuclear, electron-rich, transition metal-containing fragments, or they form either dinuclear or polynuclear metal complexes.[27] The most common examples are benzyne-metal complexes. As an example aryne-zirconocene complex **(32)** can be accessed by reaction of $ZrCp_2Cl(Me)$ with aryllithium **(33)** at elevated temperature (Figure 1.12).[28] Complex **(33)** can further react with acetonitirile to produce corresponding matallocycles.

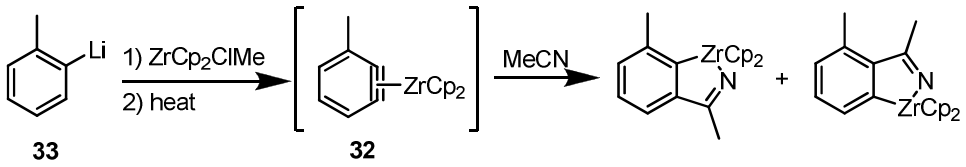

Figure 1.12. *Formation of aryne-zirconocene complex.*

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In similar fashion, treatment of $TaCp^*Me_3Cl$ with phenyllithium **(34)** produces $TaCp^*(C_6H_5)Me_3$ **(35)**, which upon heating to 120 ^oC has been shown to undergo elimination of methane to produce the benzynetantalum complex **(36)** (Figure 1.13).[29] Benzynetantalum complex **(36)** was reported to be air-stable and was characterized by X-ray crystallography. The same procedure was utilized to arrive at niobium analogue of complex **(36)**. Other examples of benzyne-tantalum complexes generated in similar manner have also been reported.[30]

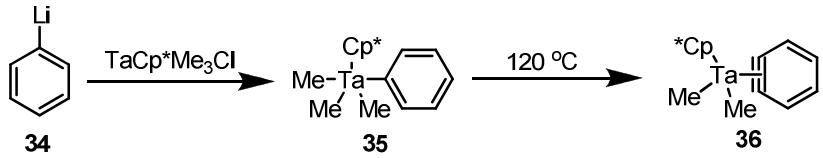

Figure 1.13. *Formation of benzyne-tantalum complex.*

Late transition metal complexes of benzynes also have been reported. Friedman and co-workers have proposed that benzyne **(17)**, generated by heating benzene-diazonium-2-carboxylate **(16)** can undergo complexation with $AgClO_4$ to form silver-benzyne complex **(37)** (Figure 1.14).[31] They have also demonstrated that this silver-benzyne complex is more elecrophilic than benzyne itself.

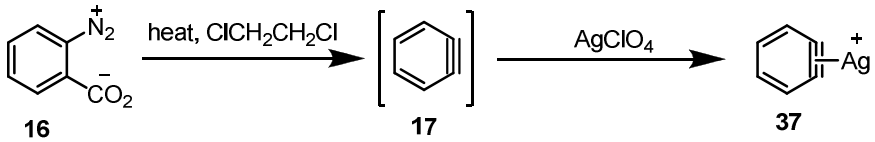

Figure 1.14. *Formation of silver-benzyne complex.*

An example of a nickel-benzyne complex has been provided by Bennett and co-workers.[32] By reacting ethylene-nickel complex **(38)** with 1,2-dibromobenzene in presence of LiCl, they were able to isolate bromophenylnickel complex **(39)**. When this complex was

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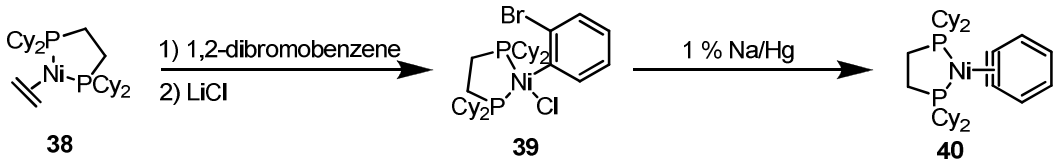
reacted with 1 % sodium amalgam it produced the intended nickel-benzyne complex **(40)** as a yellow crystalline solid (Figure 1.15). The structure of the nickel-benzyne complex **(40)** was confirmed by X-ray crystallography.

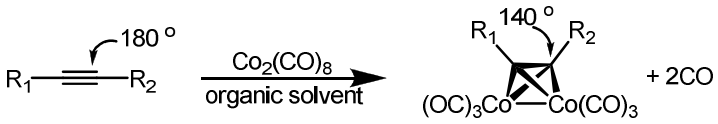


38 **39** **40**

Figure 1.15. *Formation of nickel-benzyne complex.*

1.2 Nicholas reaction

Dicobalt octacarbonyl readily reacts with alkynes **(41)** at room temperature to produce hexacarbonylalkynedicobalt complexes **(42)** (Figure 1.16). This area has been well explored and hundreds of different examples are known today.[33,34]



41 **42**

Figure 1.16. *Complexation of alkyne by dicobaltoctacarbonyl.*

This complexation reaction tends to be very versatile. It proceeds in many different types of organic solvents and is typically carried out at room temperature. Hexacarbonylalkynedicobalt complexes are normally dark red solids or liquids, and are usually air-stable for extended periods of time. These complexes can also be purified easily by crystallization or chromatography. The scope of the complexation reaction has been extended to include, but is not limited to, terminal alkynes, and various symmetrical and unsymmetrical alkynes containing carbon, cyclic alkynes, diynes, triynes, and poly-ynes.[33]

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Only severely sterically hindered alkynes tend to not undergo complexation with dicobalt octacarbonyl.[35]

Nicholas and co-workers have demonstrated the generation and the evaluation of stability of carbocation centre α- to the hexacarbonylalkynedicobalt complex **(43)**.[36] This was achieved initially during the acid catalyzed dehydration of alcohol centers α- to the hexacarbonylalkynedicobalt complex by reacting **(44)** with trifluoroacetic acid (TFA) (35 mol %) in benzene. The elimination product **(45)** was obtained in a 72 % yield (Figure 1.17). Following the discovery of the Nicholas reaction, the scope was expanded to include several different alcohol substrates. It should be noted that diol substrates containing hydroxy groups at both ends of the hexacarbonylalkynedicobalt complex tend to undergo elimination on both sides.

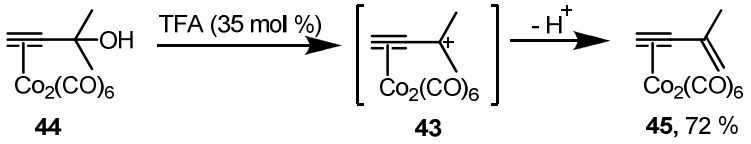

Figure 1.17. *TFA catalyzed Nicholas reaction.*

The propargylium hexacarbonyldicobalt cation does not undergo the elimination reaction in the presence of a nucleophile, but rather undergoes nucleophilic attack.[37] Hexacarbonylalkynedicobalt complex **(46)** will react with an appropriate acid source to produce the corresponding carbocation, and in the presence of anisole will undergo nucleophilic attack to generate a mixture of products **(47)** and **(48)** (Figure 1.18). It is evident from the results that sterics play an important role in the ratio of products formed. Product **(48)** becomes more prevalent as the steric bulk around the carbocation intermediate is

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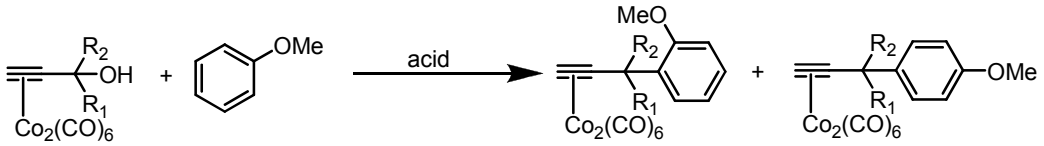
increased. It is worthy to note that TFA and HBF_4-OMe_2 were used in stoichiometric quantities in all cases.



46		47	48
R_1=R_2=H	TFA	31 %	46 %
R_1=R_2=H	HBF_4-OMe_2	35 %	49 %
R_1=Me, R_2=H	HBF_4-OMe_2	25 %	53 %
R_1=R_2=Me	HBF_4-OMe_2	--	78 %

Figure 1.18. *Reaction of anisole with hexacarbonylalkyne-dicobalt cation complex.*

Generation of the carbocation α- to the hexacarbonylalkyne-dicobalt complex is not limited to dehydration of alcohol by an acid source. It can also be accomplished by subjecting ethers, esters, acetals, aldehydes, epoxides or cyclic esters to Lewis acids, or chlorides to $AgBF_4$. The reaction of alkenes with an electrophile will also yield the intended carbocations.[38] Besides electron-rich arenes, nucleophiles also include hydrides, fluorides, beta-dicarbonyls, silyl enol ethers, silyl ketene acetals, enol borinates, enol acetals, allyl silanes, allyltins, and variety of oxygen, nitrogen and sulphur nucleophiles.[38,39]

1.3 Propargyldicobalt cation structure and properties

The hexacarbonylpropargyldicobalt cation is stabilized by interaction with an electron-rich cobalt center.[40] IR spectroscopy was used to obtain evidence of charge delocalization into the $Co_2(CO)_6$ fragment, where it was observed that the stretching frequency of the carbonyl group was 40-60 cm^{-1} higher than the corresponding neutral complex. This is indicative of decreased cobalt-carbonyl back donation due to an increase in

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positive charge on the cobalt centers. NMR studies performed by Schrieber describe two fluxional processes, which were consistent with the stabilization of the propargylic cation through the metal centers (Figure 1.19).[41] The first process is low energy (10 kcal/mol) anatarafacial migration of the carbocation from one side of cobalt center to the other, which results in enantiomerization. The second process suprafacial migration is higher in energy (13 kcal/mol) and involves 180 ^{o} rotation of the carbocation.

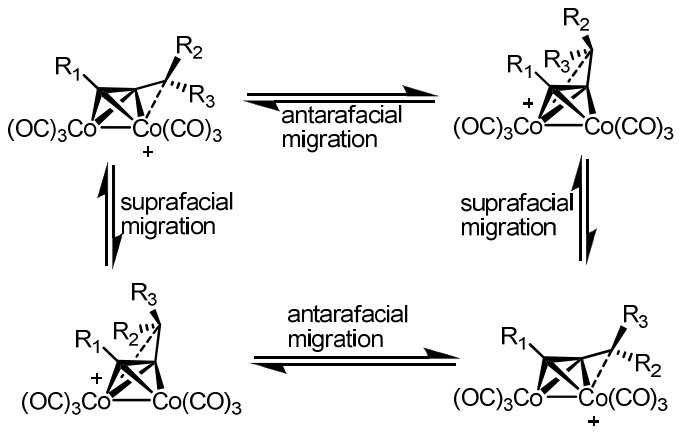

Figure 1.19. *Two fluxional processes by hexacarbonylpropargyldicobalt cation.*

Due to the difficulty of isolation, only a limited number of hexacarbonylpropargyldicobalt cation X-ray structures are available.[42,43] The Melikyan group was able to doubly complex triyne **(49)** with $Co_2(CO)_8$ to form bis(hexacarbonylalkyne)tetracobalt complex **(50)**. Subjecting complex **(50)** to the reaction with HBF_4 resulted in the formation of bis(hexacarbonylalkyne)tetracobalt complex propargyl cation **(51)** with BF_4^- as the counterion (Figure 1.20). The cation **(51)** is extensively stabilized due to the fact that there are two metal-alkyne moieties α- to the cationic centre. This resulted in good thermal stability of the salt **(51)** under aerobic conditions, which allowed the group to obtain the X-ray crystal structure. The X-ray structure revealed a nearly planar geometry about cationic carbon (out-of-plane <0.5 ^{o}) and nearly

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ideal trigonal planar arrangement (119 – 121 ^{o}). Due to the increased s-character in hybrid orbitals, the covalent bonds around the cationic centre are shortened. The covalent bond lengths of the cationic centre to the coordinated triple bonds decrease by 0.02 – 0.04 Å, however the uncoordinated alkyne bond length decreases by almost 0.10 Å.

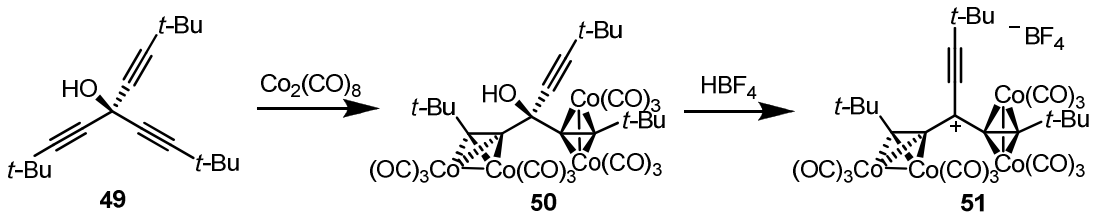

Figure 1.20. *Formation of the stabilized dodecacarbonylalkynepropargyldicobalt cation.*

1.4 Cyclohexynedicobalt complexes

To date cyclohexynedicobalt complexes are the smallest cyclic systems of cycloalkyne-dicobalt complexes known. Due to their limited stability there are only a few examples present in the literature.[44] The first example was provided by Schreiber, where exposing complex **(52)** to BF_3-OEt_2 in dichloromethane formed cyclohexyne-dicobalt complex **(53)** in 55 % yield.[45] There was no mention of the stability of the newly formed species. Subjecting complex **(54)** to the reaction with TBDMSOTf and EtN^iPr_2 in dichloromethane did not afford the intended aldol product, but instead formed cyclopentadineylallene complex **(55)** in a 63 % yield as a 1:1 mixture of isomers (Figure 1.21). Once again, there was no further investigation into the stability of the newly formed complex. Iwasawa and coworkers have utilized the Schreiber methodology to synthesize naphthalyne-dicobalt complexes; however, stability in air seems to be an issue.[44]

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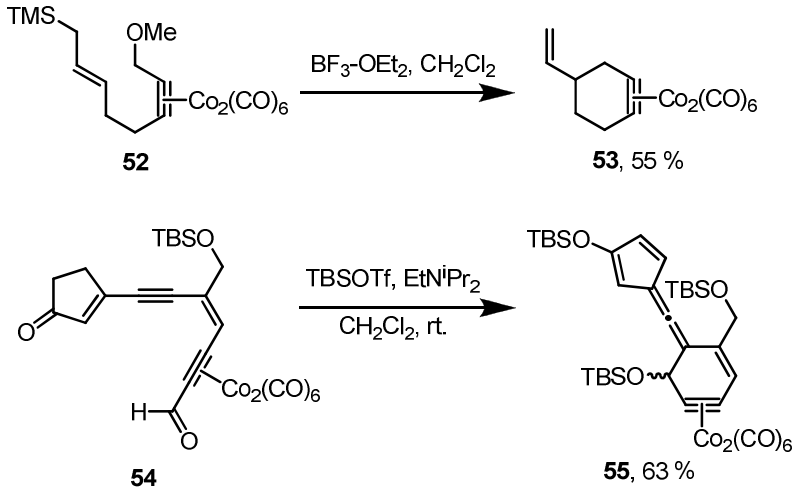

Figure 1.21. *Examples of cycloxehynedicobalt complexes.*

1.5 Cycloheptynedicobalt complexes

There have been several X-ray structures of cycloheptynedicobalt complexes reported. [42,46,47] The X-ray structure of cycloheptynonedicobalt complex **(56)** (Figure 1.22) reveals valuable data, demonstrating that the seven-membered ring is nearly planar and alkyne bond angles are approximately 138 ^{o} and 129 ^{o}, which are considerably smaller than the corresponding average value of an acyclic alkyne complex (ca. 140 ^{o}). The most notable feature of complex **(56)** is that carbonyl IR stretching frequency is exceptionally low (1579 cm $^{-1}$), which suggests strong electron back donation from the alkyne-Co_2dppm to the carbonyl groups.

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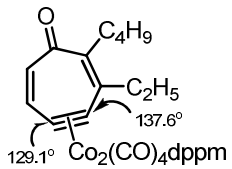
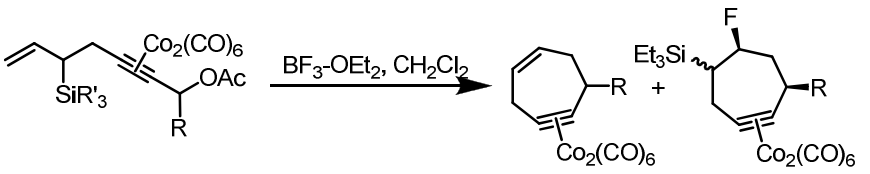


57

Figure 1.22. *Cycloheptynonedicobalt complex.*

There are many examples of cycloheptynedicobalt complexes being synthesized in a variety of different ways.[48-50] Due to their stability and ease of handling these molecules have also been utilized as precursors in the synthesis of natural products containing seven-membered ring systems. Schreiber has managed to utilize the Nicholas reaction to synthesize a seven-membered ring adduct by a similar method to that utilized to syntheisze cyclohexynedicobalt complex system (Figure 1.17).[45] The Nicholas reaction also has been utilized by the Green group, where slow addition of excess of BF_3-OEt_2 to cobalt complex **(58)** at low concentration afforded cycloheptyne-dicobalt complex **(59)** in good yield.[51] In cases where methyl and phenyl functional groups are present, small amounts of fluorocycloheptyne-cobalt complex **(60)** were isolated (Figure 1.23). The complexes are reported as being red-violet oils of good thermal stability.



58

R' = Me, R = H

R' = Et, R = H

R' = Et, R = Ph

R' = Et, R = Me

59

R = H, 89 %

R = H, 87 %

R = Ph, 84 %

R = Me, 85 %

60

R = Ph, 8 %

R = Me, 6%

Figure 1.23. *Cycloheptynedicobalt complexes from allylsilane precursors.*

References start on page 35.

Allylsilane precursors towards the synthesis of cycloheptynedicobalt complexes have been explored further, in particular to investigate the production of fluorocycloheptynedicobalt complexes.[52] The generation of halocycloheptynedicobalt complexes also provided a new pathway towards the incorporation of an aryl substituent in place of a halogen by utilizing a benzenoid solvent.[53]

Ingenol **(61)** has been previously synthesized by proceeding through the cycloheptyne-dicobalt intermediate **(64)**, which was prepared by a Nicholas reaction (Figure 1.24).[54] An alcohol **(62)** was subjected to a series of organic transformations over nine steps to arrive at the hexacarbonylalkyne-dicobalt complex **(63)**. Reacting this precursor with methylaluminum bis(2,6-dimethyl-4-nitrophenoxide) in CH_2Cl_2 afforded cycloheptynedicobalt intermediate **(64)**, which contains the backbone structure of ingenol. In nineteen synthetic steps ingenol **(61)** was synthesized starting from complex **(64)**. The yield for the cyclization reaction was not reported, since the crude material was immediately subjected to the decomplexation reaction with lithium metal and ammonia. The yield over the two steps was reported to be 67 %.

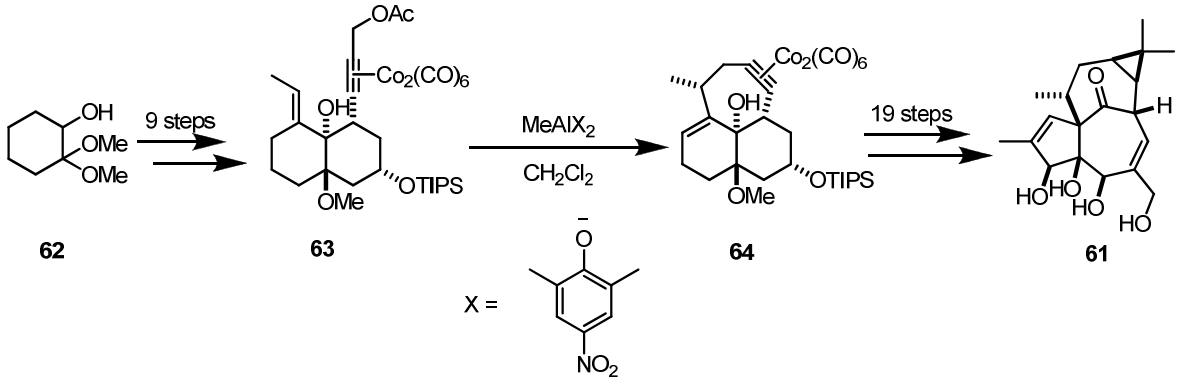


Figure 1.24. *Synthesis of ingenol through cycloheptynedicobalt intermediate.*

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When subjecting the bis(hexacarbonylalkyne)tetracobalt complex **(65)** to a reaction with excess HBF_4 in the absence of a nucleophile, cycloheptadiynetetracobalt complex **(66)** was the sole product isolated (Figure 1.25).[46] It is believed that this reaction proceeded through a mono-elimination product **(67)** which generates an intermediate carbocation complex **(68)**. At this point cyclization and elimination reactions take place to yield the cycloheptadiynetetracobalt complex **(66)** in a quantitative yield. The ring strain in the seven-membered diyne-containing ring would make the system very unstable. However, it is believed that conjugation of the alkyne units and the vinyl group along with the gem-dimethyl effect increases the ring stability to some extent. The presence of oxygen or sulfur based nucleophiles does not hinder the reaction, but serves to increase the rate of the reaction by facilitating proton abstraction.

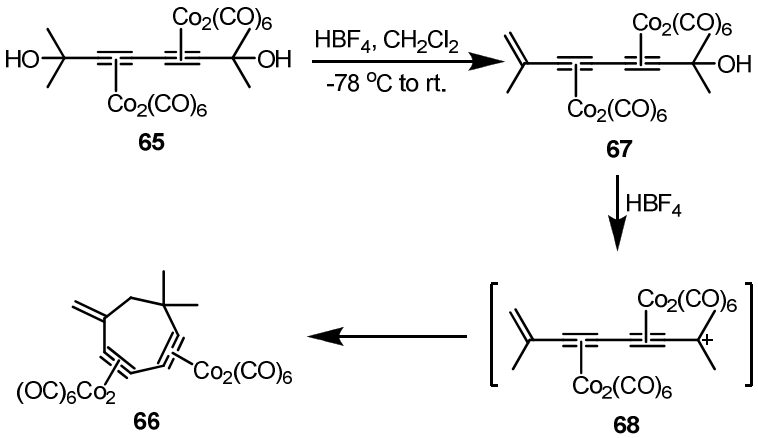

Figure 1.25. *Nicholas reaction in formation of cycloheptadiynetetracobalt complex.*

Using the intramolecular Nicholas reaction, the Green group has managed to synthesize a variety of benzocycloheptynedicobalt complexes (Figure 1.26).[50] For example, a process where arylaldehyde **(69)** was very efficiently converted to the dibromoalkene **(70)**, followed by a stereoselective palladium catalyzed reduction of the *trans* carbon-bromine

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bond of dibromoalkene **(70)** and a subsequent Sonogashira coupling of the remaining *cis* bromide with propargyl alcohol produced Z-enyne-propargyl alcohol **(71)**. Subjecting the alcohols to a two-step reaction with acetic anhydride-pyridine mixture, followed by a reaction with dicobalt octacarbonyl gave rise to hexacarbonylalkynedicobalt species **(72)**. A Lewis acid mediated cyclization of precursor **(72)** gave the intended benzocycloheptynedicobalt complex **(73)**. A variety of substitution patterns on the phenyl ring could be employed, and it was also proven that this reaction was also viable with thienyl, furyl and indole systems. It should be noted that cyclization yields range from 49 – 90 %, with thienyl and indole systems giving mixtures of regioisomers.

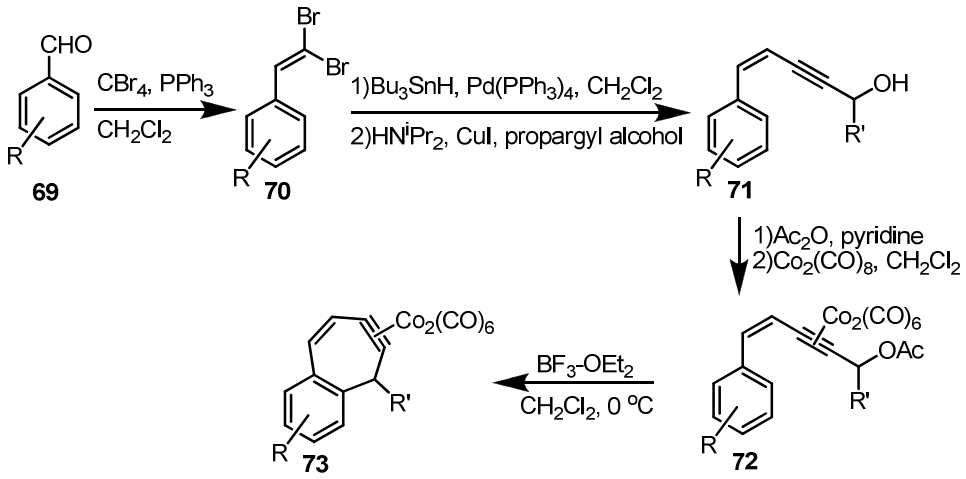

Figure 1.26. *Benzocycloheptynedicobalt complexes by intramolecular Nicholas reaction.*

Similar types of systems have been generated by vinylogous Nicholas reactions, generating 6-7-5-, 6-7-6- and 6-7-7- ring systems **(79)** (Figure 1.27).[55] The precursor to the cyclization reaction, hexacarbonylalkynedicobalt complex **(78)**, was synthesized by a Sonogashira coupling reaction between a terminal alkyne **(74)** and vinyl bromide **(75)** to generate an alkyne tethered bicyclic system **(76)**. The aldehyde was then reduced to the corresponding alcohol and reacted with an acetic anhydride and pyridine to form the acetate

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(77), which was in turn complexed to make precursor complex **(78)**. The BF_3-OEt_2 mediated cyclization of **(78)** gave rise to the tricyclic system **(79)**. Yields for these vinylogous Nicholas reaction based cyclizations for this particular case range from 40-90 %.

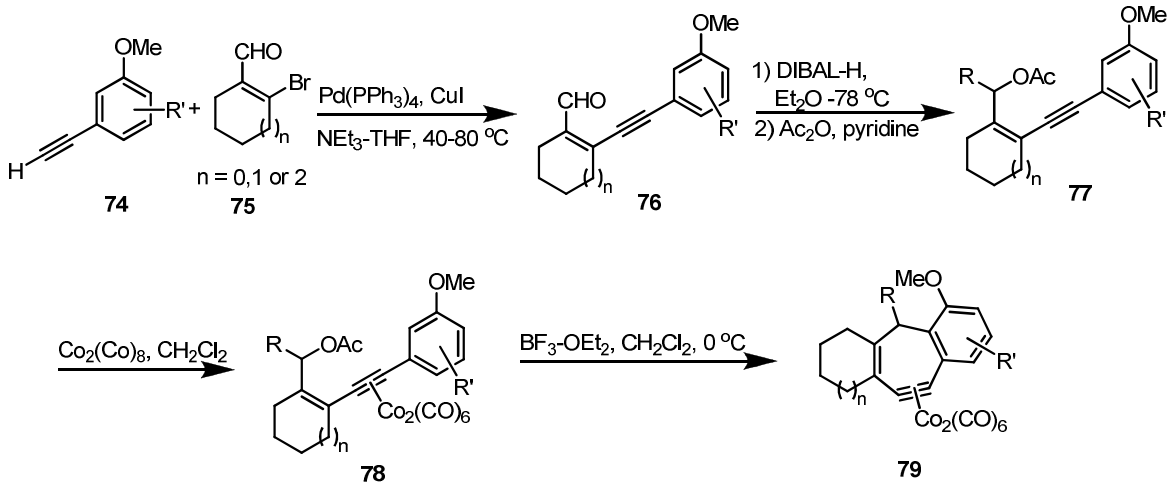

Figure 1.27. *Vinylogous reaction in formation of benzocycloheptynedicobalt complexes*

Incorporating electron rich arenes as successful nucleophiles in Nicholas reactions allowed for the synthesis of dibenzocycloheptynedicobalt complex **(83)**. Access to this backbone structure ultimately lead to the synthesis of allocolchicine NSC 51046 **(84)** and derivatives, along with the formal synthesis of (-)-allocolchicine **(85)** (Figure 1.28).[56] Hexacarbonylalkynedicobalt complex **(82)** was prepared mainly through the Suzuki coupling reactions of aryl bromides containing an aldehyde at the *ortho* position with arylboronic acid precursors. The aldehydes **(80)** were then converted to the propargyl alcohol species **(81)** by means of Corey-Fuchs reactions, which were in turn reacted with acetic anhydride and pyridine to form a propargyl actate intermediate. This intermediate was then complexed with $Co_2(CO)_8$ to generate complex **(82)**. A Lewis acid mediated cyclization then affords dibenzocycloheptyne-dicobalt complexes **(83)**. With intent to scavenge any acid liberated during the cyclization reaction, EtN^iPr_2 was used along with BF_3-OEt_2. Several derivatives of

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dibenzocycloheptynes were synthesized, with yields between 56 – 91 % for the intramolecular Nicholas reaction.

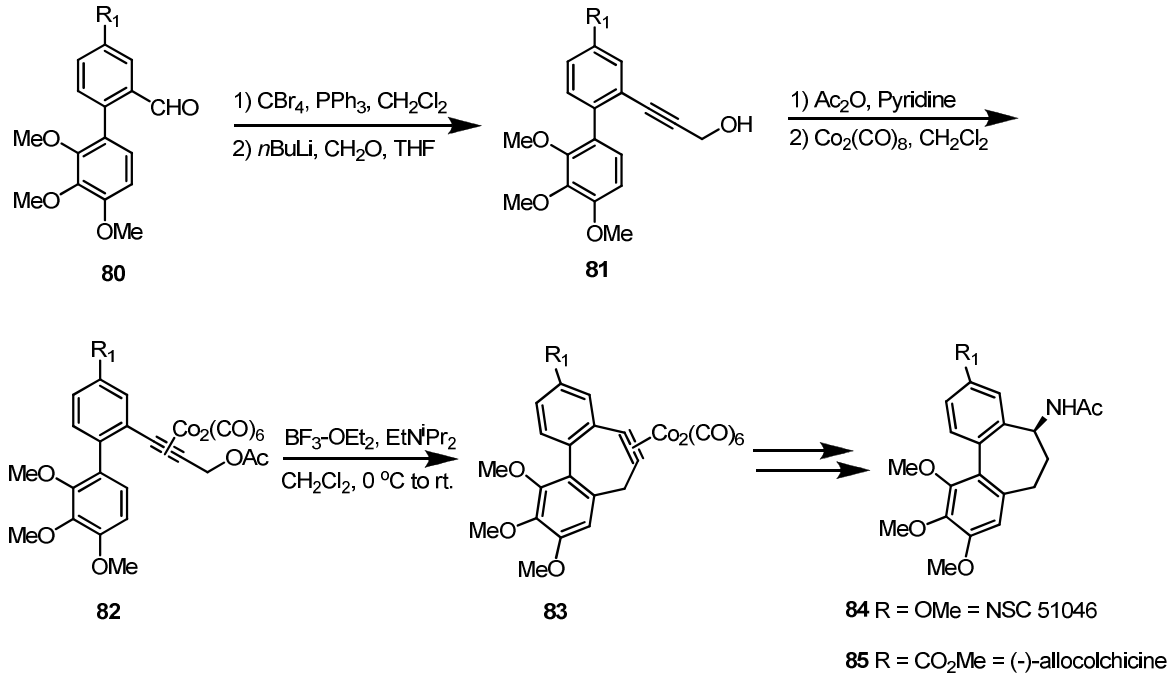

Figure 1.28. *Dibenzocycloheptynedicobalt complex generation by intramolecular Nicholas reaction.*

Nicholas type reactions are not the only way to access cycloheptynedicobalt complexes. Ring-closing metathesis has also shown to be a reliable way to synthesize such systems.[57,58] To prove the viability of ring-closing metathesis in this case, hexacarbonylalkynedicobalt complexes **(86)** were reacted with Grubbs I catalyst $(Cy_3P)_2Cl_2Ru{=}CHPh$ (10 mol %) to produce a variety of cycloheptynedicobalt complexes **(87)** in moderate to excellent yields (Figure 1.29).[57,58]

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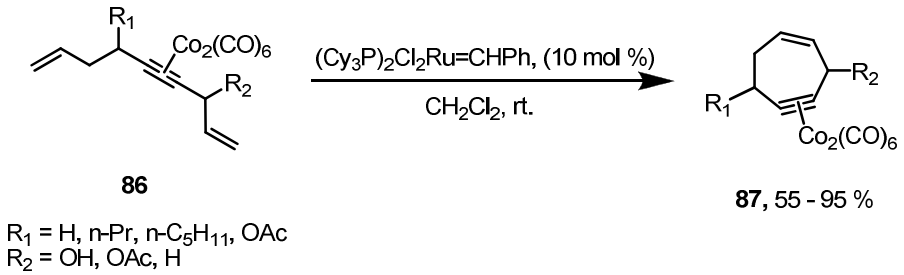

86

R_1 = H, n-Pr, n-C_5H_{11}, OAc
R_2 = OH, OAc, H

87, 55 - 95 %

Figure 1.29. *Ring-closing metathesis in construction of cycloheptynedicobalt complex.*

The initial trial for this RCM reaction was carried out with no substitution at R_1 position, and an alcohol function at R_2 position; unfortunately only 10 % conversion was observed. Incorporating combinations of different functional groups at R_1 and R_2 positions, and protecting the alcohol, lead to increased yields. Attempts at cyclization of cycloheptynedicobalt complex with the Schrock catalyst $Mo(C_{10}H_{12})(C_{12}H_{17}N)[OC(CH_3)(CF_3)_2]_2$ were not successful.

The Iwasawa group have demonstrated that cycloheptynedicobalt complexes can also be generated by silica gel or Lewis acid mediated Diels-Alder reactions (Figure 1.30).[59,60] When placed on to a silica gel column under inert atmosphere, complex **(88)** underwent [4+2] cycloaddition reaction to elute residual complex **(88)** and the Diels-Alder product **(89)** in a 90 % yield as 1 : 10 mixture, respectively.

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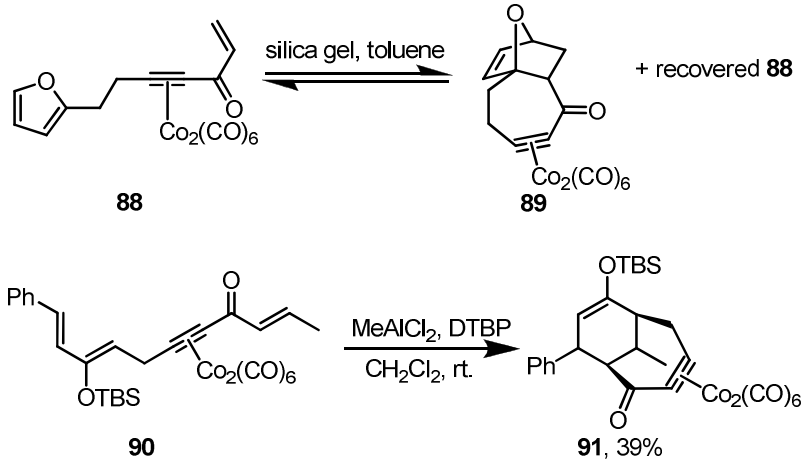

Figure 1.30. *Diels-Alder reaction in cycloheptynedicobalt synthesis.*

Complex **(88)** and **(89)** tend to undergo slow equilibration in a $CDCl_3$ solution to give a 7 : 3 mixture of **(88)** to **(89)** after 3 days at room temperature. When hexacarbonylalkyne-dicobalt complex **(90)** was subjected to Lewis acid mediated Diels-Alder reaction, bridged-type [4+2] cycloaddition complex **(91)** was obtained in a 39 % yield. A lower yield obtained for **(91)** might be the result of the severe strain in the system, since systems with the less strained (bicyclo[5.3.1]undecyne) produce higher yield.

The Heck reaction is another useful tool in the synthesis of cycloheptynedicobalt complexes (Figure 1.31).[47] Due to the instability of alkyne-$Co_2(CO)_6$ complexes at elevated temperatures[61] hexacarbonylalkynedicobalt complex **(92)** was subjected to ligand exchange with diphenylphosphinomethane (dppm) to make a more thermally stable alkyne-$Co_2(CO)_4$-dppm complex **(93)**. A palladium-catalyzed carbonylative Heck reaction was then performed on this complex at elevated temperatures to produce a cycloheptynedicobalt complex **(94)** in moderate yield.

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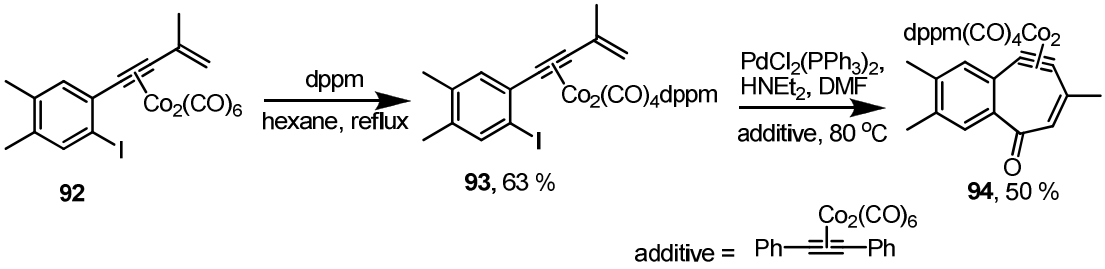

Figure 1.31. *Cycloheptynonedicobalt complexes by carbonylative Heck reaction.*

It is also noteworthy to mention that Tanino and coworkers have utilized Hosomi-Sakurai/Mukaiyama reactions to form cycloheptynedicobalt complexes.[42,62] Finally, a single example exists of a Michael reaction to synthesize a cycloheptynedicobalt complexes; as was demonstrated by Iwasawa and coworkers.[44]

1.6 Cyclooctynedicobalt complexes

Even though they are not as common as cycloheptynedicobalt complexes, examples of the synthesis of cyclooctynedicobalt complexes are present in the literature. Ring-closing metathesis of diene complex **(95)** under the same conditions described in Figure 29 produced the cyclooctynedicobalt complex **(96)** in a 76 % yield (79 % based on recovered starting material **(97)**) (Figure 1.32).[57]

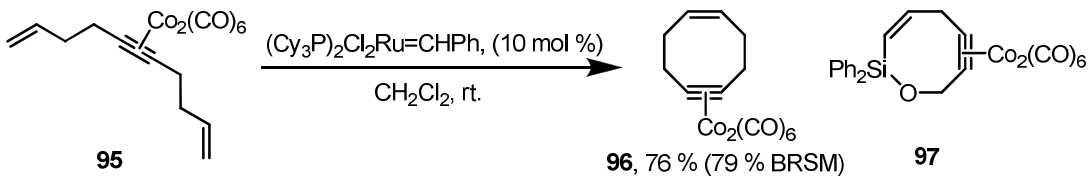

Figure 1.32. *Cyclooctynedicobalt complex synthesis by ring-closing metathesis.*

It is also possible to incorporate different functional groups such as: -OH, -OAc, -OTBS or a ketone, α- to the hexacarbonylalkynedicobalt moiety, and by using a similar set of reaction

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conditions the substituted cyclooctynedicobalt complexes can be obtained.[58] Heterocyclic cyclooctynedicobalt complex **(97)** can be prepared in a similar fashion in a moderate yield using 2,6-diisopropylphenylimidoneophylidene-molybdenum(VI) bis(hexafluoro-tert-butoxide) (52 mol %) as catalyst.[58]

Bridged-bicyclic cyclooctyne systems of bicyclo[5.3.1]undecyne type **(98)** can be synthesized in a similar manner to that utilized for the bridged bicyclo[4.3.1]decyne system **(91)**. A Lewis acid mediated intramolecular [4+2] cycloaddition of hexacarbonylalkynedicobalt complex **(99)** afforded the intended bridged system **(98)** in a moderate yield (Figure 1.33).[60] In some cases, the silyl enol ether adducts converted to the corresponding ketone in situ. In order to expand the scope of this reaction, an example of a bridged bicyclo[6.3.1]dodecyne system was generated in a similar fashion in a moderate yield.

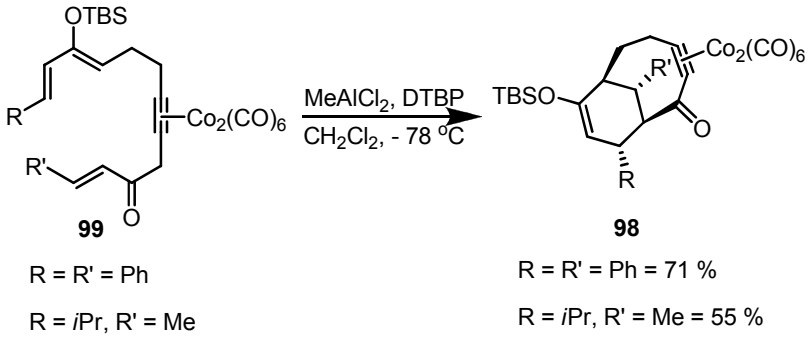

Figure 1.33. *Bicyclo[5.3.1]undecynedicobalt complex synthesis by [4+2] cycloaddition.*

The Iwasawa group has subjected different derivatives of silyl enol ether complexes **(100)** to $MeAlCl_2$ mediated Michael type cyclization reaction to obtain cyclooctynedicobalt complexes **(101)** in moderate yields. In the case where R_2 is ethyl substituted, a small amount (10 %) of the silyl enol ether adduct was converted to the corresponding ketone **(102)** in situ (Figure 1.34).[42]

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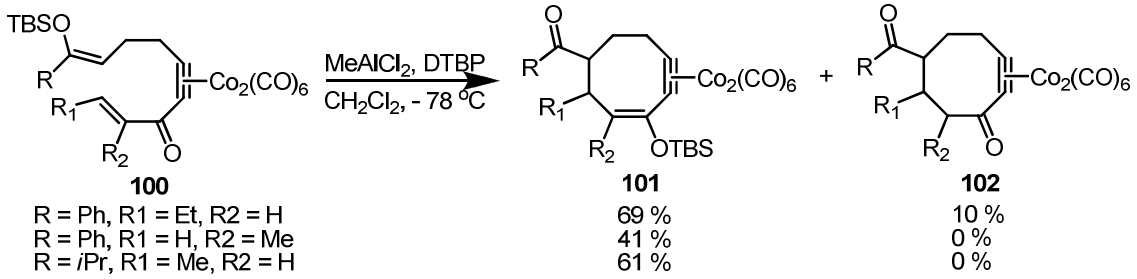

Figure 1.34. *Cyclooctynedicobalt complexes by Lewis acid mediated Michael-type reactions.*

The [5+2] cycloaddition reaction of silyl enol ether **(103)** with hexacarbonylalkynedicobalt complex **(104)** under the influence of $EtAlCl_2$ produced the desired cycloheptynonedicobalt complex **(105)** in an excellent yield and good diastereoselectivity.[42] Regardless whether the silyl enol ether possesses (Z) or (E) configuration, a single diastereomer was isolated. A one-carbon ring expansion reaction, mediated by $TMSCHN_2$ in the presence of $EtAlCl_2$, gave rise to cyclooctynonedicobalt complex **(106)** in a good yield (Figure 1.35). The incorporation of a methylene group almost exclusively occurred at the opposite side of the bulky alkynedicobalt complex moiety.

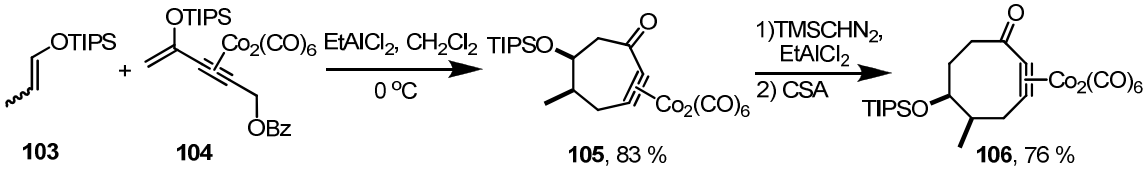

Figure 1.35. *Cyclooctynonedicobalt complex via a one-carbon ring expansion reaction.*

In order to avoid the ring expansion reaction, a formal [6+2] cycloaddition reaction can be carried out to synthesize cyclooctynonedicobalt complexes such as **(106)**[63] by using silyl enol ether **(104)** type precursors with an extra methylene spacer between the alkyne carbon and silyl enol ether. The same set of conditions utilized as for [5+2] cycloaddition reaction

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(Figure 1.35), and the corresponding products were obtained in good yields and excellent diasteroselectivity.

Nagumo and coworkers have efficiently utilized the Friedel-Crafts reaction to synthesize cyclooctynedicobalt complexes.[64] In the presence of BF_3-OEt_2, vinyloxirane complex **(107)**, underwent a Friedel-Crafts cyclization reaction and generate cyclooctyne complexe **(108)** in good yields (Figure 1.36). It should be noted that this reaction proceeds with complete regioselectivity on the arene ring. Unfortunately, construction of nine-membered adducts by these conditions was unsuccessful and only degradation products were obtained.

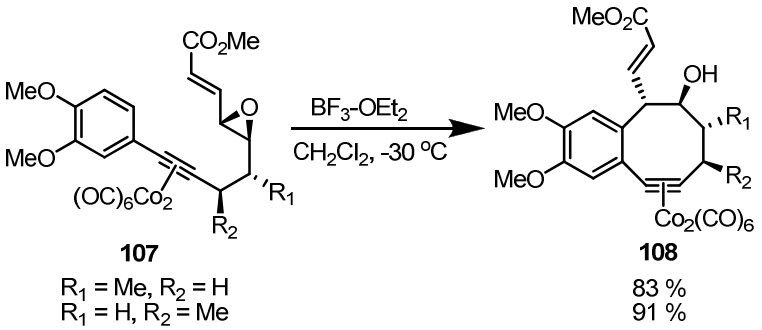

Figure 1.36. *Friedel-Crafts approach to cyclooctynedicobalt complex.*

1.7 Removal of $Co_2(CO)_6$ moiety

In most cases removal of the hexacarbonyldicobalt moiety from an alkyne is desirable in order to proceed with the synthesis, especially that of a natural product. Reductive decomplexation reaction has proven to be a very viable route to accesses corresponding alkenes from a hexacarbonylalkynedicobalt. Bu_3SnH is the most common reagent utilized to carry out this procedure.[42,63,64] Introducing Bu_3SnH into a reaction mixture containing

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cyclooctynonedicobalt complex **(109)** in toluene produced the corresponding decomplexed alkyne compound **(110)** in good yields. A second type of reductive decomplexation involves a two-step process utilizing Et_3SiH and TFA.[44,56,65] When cycloheptyne-dicobalt complex **(111)** is reacted with triethylsilane in the presence of bis(trimethylsilyl)acetylene it undergoes transfer of hexacarbonyldicobalt moiety on to a scavenger alkyne and forms a vinylsilane intermediate. Upon the addition of TFA, dibenzocycloalkene **(112)** is formed in situ, in excellent yield. A less common reductive decomplexation can be accomplished by using sodium hypophosphite.[60,61] Isobe and coworkers have demonstrated that upon heating heterobicycloheptynedicobalt complex **(113)** in the presence of sodium hypophosphite, synthesis of the corresponding alkene **(114)** can be achieved in good yields (Figure 1.37). Although the mechanism has not been proven, it was proposed that upon heating the complex, homolytic cleavage of the cobalt-cobalt bond occurs. This biradical intermediate can then abstract a hydrogen radical from the sodium hypophosphite, which ultimately leads to the intended alkene product. Finally in, some instances, refluxing the hexacarbonylalkynedicobalt complex in the emulsion of water and toluene has proven to be an efficient way of performing reductive decomplexation.[44,60] The one time example of Li/NH_3 mediated reductive decomplexation of hexacarbonylalkynedicobalt complex was demonstrated in synthesis of ingenol by Tanino and co-workers (see Figure 1.24).[54]

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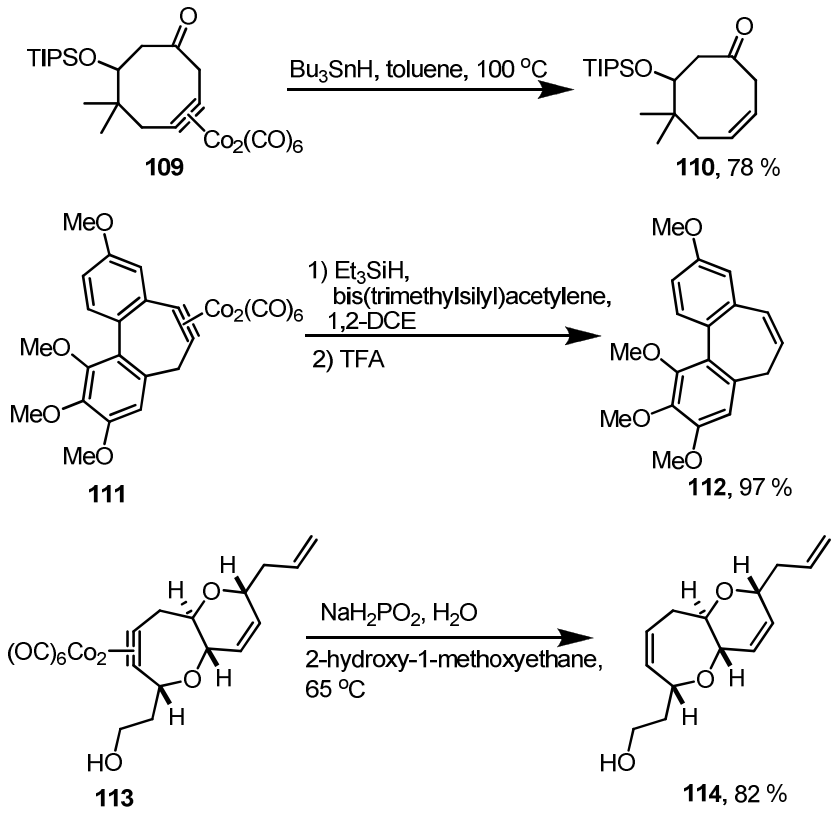

Figure 1.37. *Reductive decomplexation methods.*

Iodinative decomplexation of cycloheptynonedicobalt complex **(94)** in the presence of I_2 will generate diiodoalkene product **(115)** in moderate yields (Figure 1.38).[47] This pathway of decomplexation generates a very useful synthetic handle for any subsequent coupling reactions.

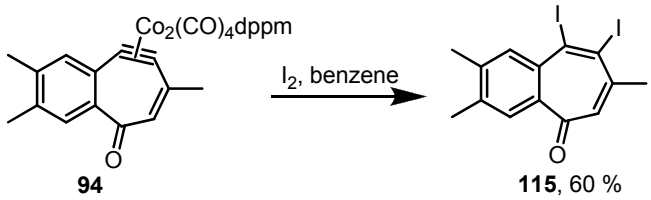

Figure 1.38. *Iodinative decomplexation of a hexacarbonylalkynedicobalt.*

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1.8 Dibenzocyclooctadiene and dibenzocycloheptadiene synthesis of natural products

Dibenzocyclooctadiene structures were first isolated form fruits of *Schizandra chinesis.* The first of these compounds to be isolated was (+)-schizandrin **(116a)**.[66] Almost three decades later (+)-isoschizandrin was isolated from the same species of fruit **(116b)**.[67] Ikeya and co-workes were also responsible for the isolation of (+)-deoxyschizandrin, also better known as schizandrin A **(117)**.[68]

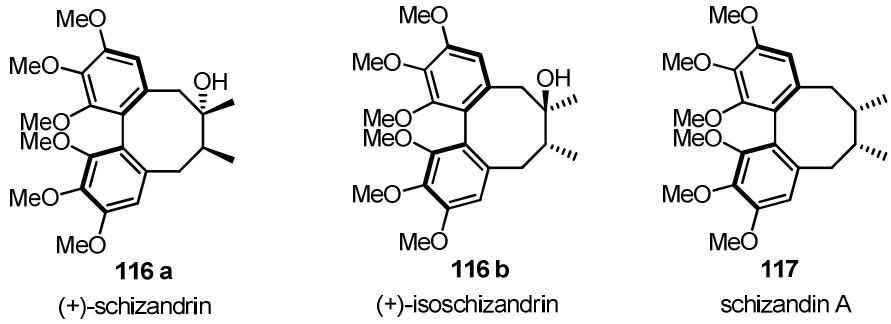

Figure 1.39. *Structures of (+)-schizandrin, (+)-isoschizandrin and schizandrin A.*

Dibenzocyclooctadiene compounds have shown to have interesting biological activities associated with them.[69,70] Anticancer activities of these compounds have also been previously reported. [71,72]

Following their discovery, these compounds have become an appealing target for total synthesis. Meyers and coworkers have managed to successfully synthesize (-)-isoschizandrin **(120)** and (-)-schizandrin **(121)**.[73] The cross-coupling reaction of the appropriate aryl bromide and chiral aryloxazoline produced the biaryl system in the proper orientation. After a series of synthetic manipulations, the precursor to cyclization reaction **(118)** was obtained. The bromo aldehyde intermediate **(118)** underwent a radical cyclization initiated by SmI_2 to produce dibenzocyclooctadiene backbone structure **(119)**. Subsequent

References start on page 35.

reaction of compound **(119)** with MeLi afforded (-)-isoschizandrin **(120)** and (-)-schizandrin **(121)** in 85 % yield as 8 : 1 mixture, respectively (Figure 1.40).

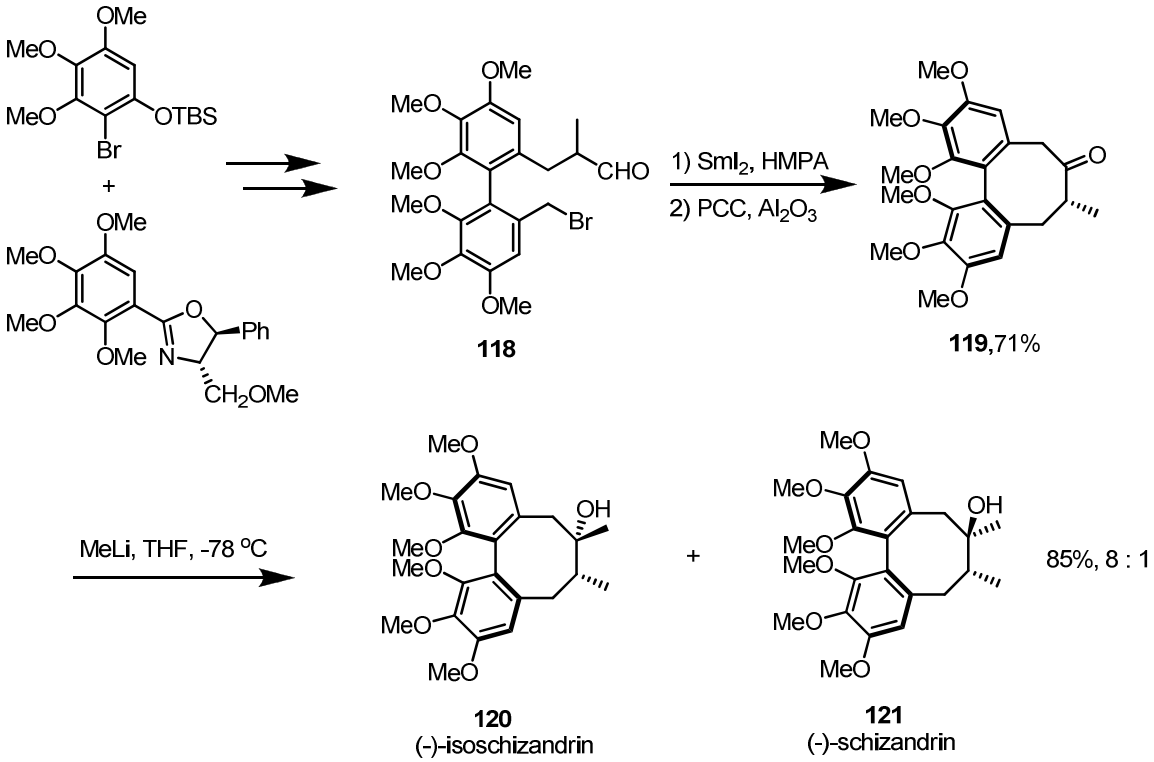

Figure 1.40. *SmI_2 mediated synthesis of (-)-isoschizandrin and (-)-schizandrin.*

Taking a different route, Wakamatsu and co-workers have managed to successfully synthesize (+)-schizandrin **(116)** (Figure 1.41).[74] After construction of the dibenzyl lactone moiety **(122)**, successful coupling of the two aryl groups by subjecting **(122)** to a reaction with $Fe(ClO_4)_3$ in presence of CF_3CO_2H in CH_2Cl_2 generated coupled product **(123)** in 90 % yield. Following the construction of the dibenzocyclooctadiene backbone **(123)**, the lactone moiety was subjected to a series of reactions which produced (+)-schizandrin **(116a)**. Gomisin A was prepared in similar fashion. This work has sparked a series of publications by the Wakamatsu group, where they have synthesized a variety of different dibenzocyclooctadiene compounds.[75-77]

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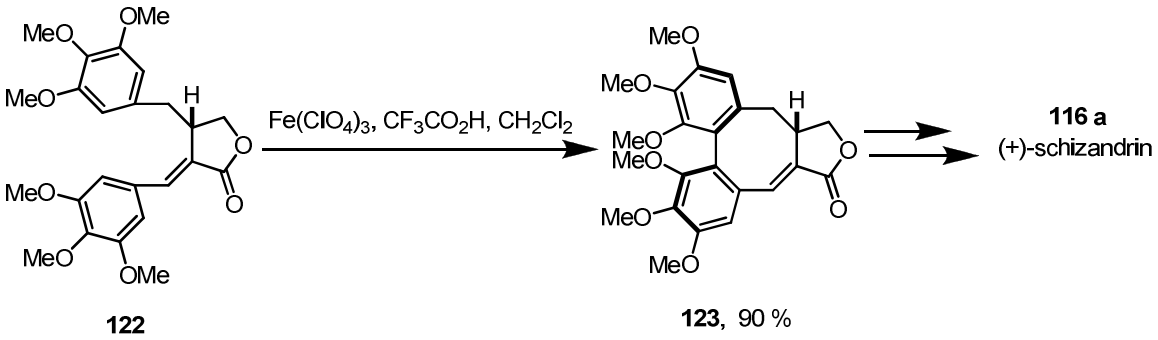

Figure 1.41. *$Fe(ClO_4)_3$ mediated aryl coupling in synthesis of (+)-schizandrin.*

Similar to this, Coleman and coworkers more recently synthesized gomisin E, gomisin R and interiotherin A by oxidative coupling of a mixed cuprate derived from two tethered aryl bromide systems **(124)**, to afford the dibenzocyclooctadiene adduct **(125)** in 69 % yield. Modification of the OTBDMS function lead to synthesis of the intended natural products (Figure 1.42).[78]

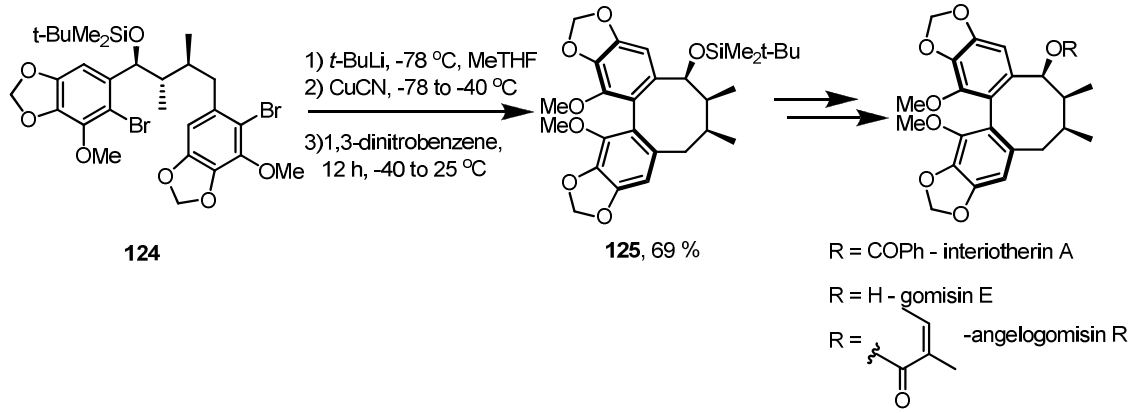

Figure 1.42. *Oxidative copper mediated coupling of aryl bromides in synthesis of interiotherin A, gomisin E and angelogomisin R.*

The total synthesis of gomisin E and therefore the formal total synthesis of interiotherin A and angelogomisin R was achieved by RajanBabu and coworkers.[79] The stereoselective borostannylation-cyclization of the axially chrial diyne **(126)** gave rise to the

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dibenzocycloodiene backbone structure **(127)** in 71 % yield (Figure 1.43), which was further modified to produce the target natural products.

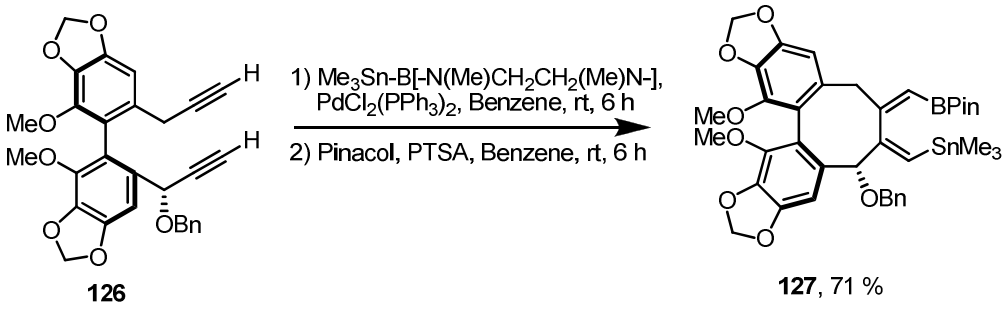

Figure 1.43. *Borostannylation-cyclization of diynes in synthesis of interiotherin A, gomisin E and angelogomisin R.*

Turning to dibenzocycloheptadienes, our attention has been drawn to the tenuifolin. The sesquiterpenoid tenuifolin itself was isolated from the stems of *Cinnamomum tenuifolium*.[80] Although tenuifolin has seen only limited synthetic attention in the literature, the total synthesis of related dibenzocycloheptadiene ring systems has been achieved.[56,81] Preliminary biological studies show that tenuifolin possesses a weak activity against the tumor cell line DU154.[80] Similar to the structure of tenuifolin, subamol and reticuol have been isolated from roots of *Cinnamomum subavenium* and *Cinnamomum reticulatum*, respectively.[82,83] Reticuol has also shown an increase in the inhibitory activity of microsome CYP3A4.[84] Microsome CYP3A4 can be related to poor drug bioavailability, various acute and chronic toxicities, cancer susceptibility and adverse drug interaction.[85]

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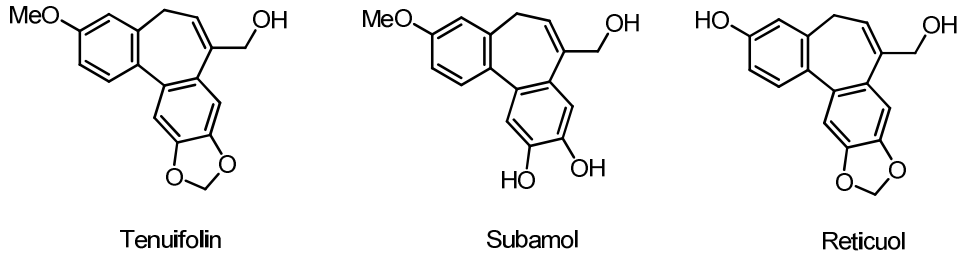

Figure 1.44. *Structures of tenuifolin, subamol, and reticuol.*

The first total synthesis of tenuifolin was reported recently by Wu and coworkers.[86] By coupling (3-methoxybenzyl) aldehyde to the appropriate benzyl bromide by means of a Reformatsky reaction, the hydroxy ester **(128)** was obtained in a 90 % yield. The dehydration of the alcohol afforded a mixture of *E*- **(129)** and *Z*- **(130)** isomers, 1 : 2 respectively. Subjecting this mixture to a PIFA mediated oxidative biaryl coupling afforded the dibenzocycloheptene product **(131)** in a 58 % yield. A DIBAL-H mediated reduction of the ester produced the desired tenuifolin **(132)** in 91 % yield (Figure 1.45).

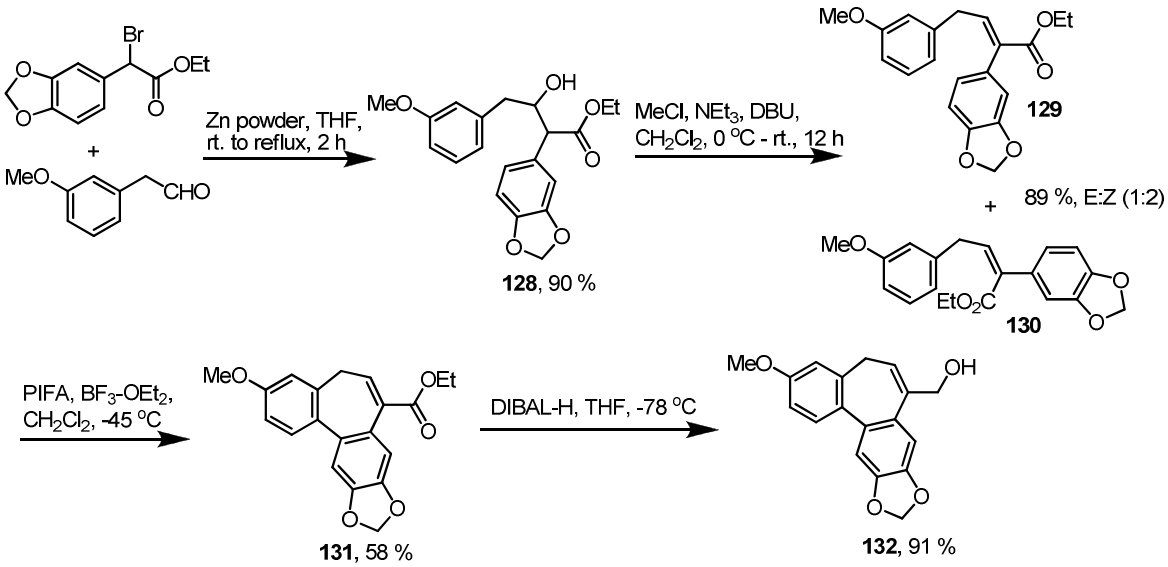

Figure 1.45. *PIFA mediated cyclization reaction in first ever synthesis of tenuifolin.*

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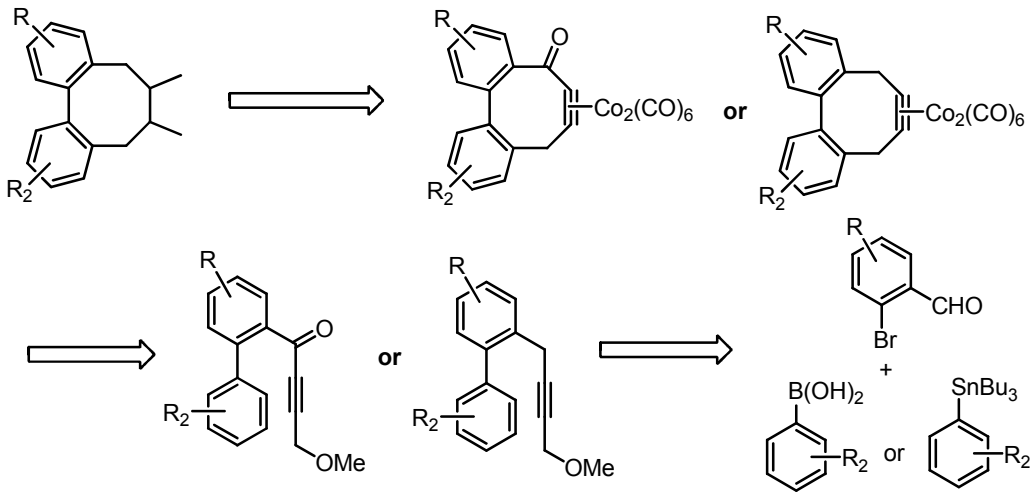
CHAPTER 2 : RESULTS AND DISCUSSION

2.1 Dibenzocyclooctadiene synthesis by Nicholas reaction

From previous research performed by the Green group, it was evident that intramolecular Nicholas reactions can be a reliable pathway towards the synthesis of dibenzocycloheptynedicobalt complexes, and which has ultimately led to the synthesis of allocolchicine NSC 51046 and the formal synthesis of (-)-allocolchicine.[1] Given the viability of cycloheptynedicobalt complexes, we considered it important to address the question of whether analogous dibenzocyclooctynedicobalt complexes could be obtained by a similar intramolecular Nicholas reaction approach. In particular, an approach involving cross-coupling to form the biaryl, modification of the aldehyde to give a propargylic ether, Nicholas cyclization and subsequent decomplexation (Scheme 2.1) appeared a promising one for the synthesis of (±)-isoschizandrin, (±)-schizandrin and (±)-schizandrin A.



Scheme 2.1. *Retrosynthetic approach to dibenzocyclooctadienes.*

Our plan involved the development of two methodologies to synthesize the dibenzocyclooctynedicobalt complex derivatives. One method was designed to ultimately

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afford the dibenzocyclooctynedicobalt complex with a carbonyl functional group adjacent to the hexacarbonylalkynedicobalt moiety. It was believed that placement of the carbonyl in the product would give an additional synthetic handle for the manipulation of the dibenzocyclooctane, and therefore give potential accesses to a wider range of compounds. However, for isoschizandrin, schizandrin, or schizandrin A, it was determined that carbonyl group at the benzylic position was not required, and this lead to another approach to synthesize dibencocyclooctyne ligands without any substitution at position adjacent to the hexacarbonylalkynedicobalt moiety.

Fuerstner conditions[2] were utilized for the Suzuki cross-coupling reactions between the aryl bromides and arylboronic acids catalyzed by $Pd(PPh_3)_4$ to generate the biaryl systems **(133)** and **(134)** in good yields (Figure 2.1). To provide a heterocyclic example, 3-thiopheneboronic acid was coupled with the 2-bromo-5-methoxyphenylboronic acid to synthesize heterocyclic biaryl system **(135)** in 79 % yield.

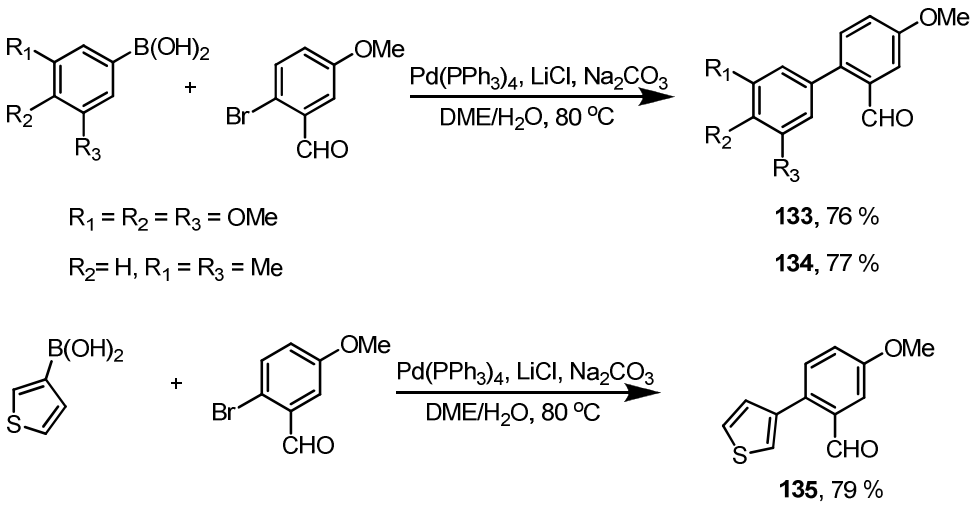

Figure 2.1. *Suzuki cross-coupling results for biaryl-2-carbaldehyde synthesis.*

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Due to the inconsistency in the purity of the 2,3,4-trimethoxyphenylboronic acid provided by the supplier, we resorted to a Stille cross-coupling reaction of tributyl(2,3,4-trimethoxyphenyl)stannane and the appropriate aryl bromide in two cases. This protocol produced the intended biaryl systems **(136)** and **(137)** in good yields (Figure 2.2). The reaction was catalyzed by $Pd(PPh_3)_4$ in presence of CuI as a co-catalyst.

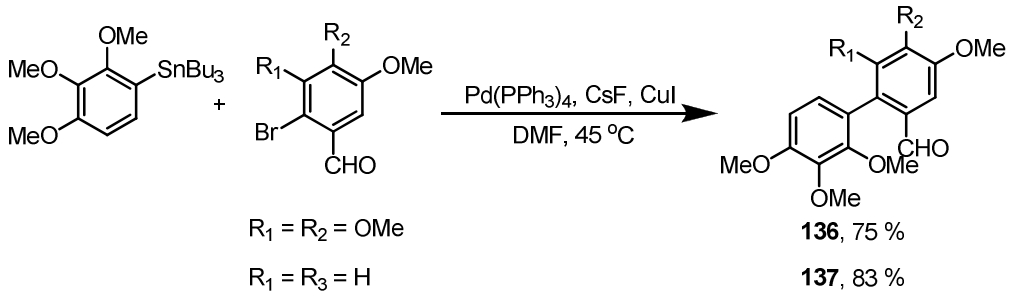
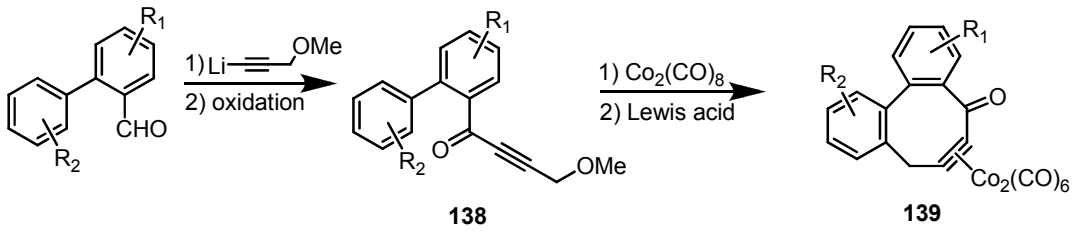


Figure 2.2. *Stille cross-coupling results in dibenzocyclooctene synthesis.*

With the biaryl systems in hand, the door had been opened to both of the two plausible synthetic pathways to synthesize dibenzocyclooctynedicobalt complexes. The first of these synthetic pathways (Scheme 2.2) involves reaction of biaryl systems with lithiated propargyl methyl ether, followed by the oxidation of the resulting alcohol to generate highly conjugated ketone **(138)**. When this system was subjected to the complexation reaction with $Co_2(CO)_8$, the corresponding hexacarbonylalkynedicobalt complexes were generated. Subjecting these compounds to Lewis acid mediated intramolecular Nicholas reaction to form dibezocyclooctynedicobalt complexes **(139)**. Other examples of these systems have been previously reported as work done during the undergraduate research;[3] however, only newly formed examples are presented in this thesis.

References start on page 73.



Scheme 2.2. *First synthetic pathway for synthesis of dibenzocyclooctynedicobalt complexes.*

Biaryl compounds **(136)** and **(137)** were utilized as the starting materials for this particular synthetic pathway. Lithiated propargyl methyl ether was generated in situ by reacting propargyl methyl ether with MeLi in THF. To this mixture was then introduced biaryl system containing an aldehyde, which acted as an electrophile to the nucleophilic acetylide. This reaction produced corresponding alcohols **(140)** and **(141)** in excellent yields (Figure 2.3).

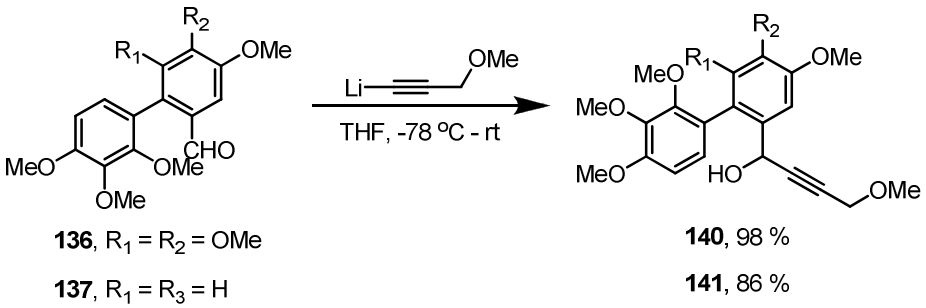


Figure 2.3. *Lithium acetylide addition results in synthesis of dibenzocyclooctynedicobalt complexes.*

In these particular cases, compounds **(140)** and **(141)** posses highly activated alcohols, which makes them good candidates for oxidation with MnO_2. Using this protocol, these alcohols formed the corresponding ketone products **(142)** and **(143)**, respectively, in excellent yields (Figure 2.4). The evidence of product formation was also apparent in the physical properties, particularly the change in color. The precursors **(140)** and **(141)** to

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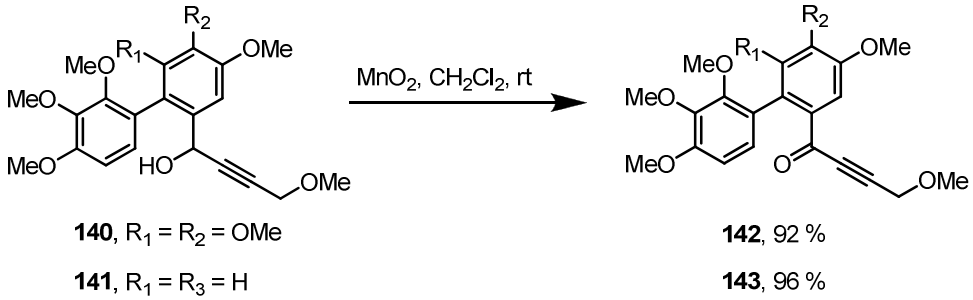
oxidation reaction existed as a colorless solid or clear viscous oil. Following the oxidation reaction, conjugation through the system is increased and final products **(142)** and **(143)** existed as yellow oils.



140, $R_1 = R_2 = OMe$

141, $R_1 = R_3 = H$

142, 92 %

143, 96 %

Figure 2.4. *MnO_2 oxidation results in synthesis of dibenzocyclooctynedicobalt complexes.*

At this point alkynes **(142)** and **(143)** were subjected to the complexation with $Co_2(CO)_8$ and the corresponding hexacarbonylalkynedicobalt complexes **(144)** and **(145)** were formed in excellent yields (Figure 2.5). Complex **(145)** was obtained as dark red crystals, while complex **(144)** had physical appearance of a dark red viscous oil. Both of these compounds were quite air stable and easily purified by chromatographic methods. The stability of these compounds began to become questionable over long-term exposure to solvents in air at temperatures above 65 ^{o}C. These compounds were therefore stored for longer periods of time at -20 ^{o}C. After one week at -20 ^{o}C, decomposition of approximately 3 % was evident with these compounds by repurification and weight measure. The effect of complexation was also evident in the ^{1}H NMR spectra. For both compounds, the resonance pertaining to protons adjacent to the hexacarbonylalkynedicobalt moiety was shifted downfield by approximately 0.5 ppm, which is indicative of a deshielding effect of the CO ligands.

References start on page 73.

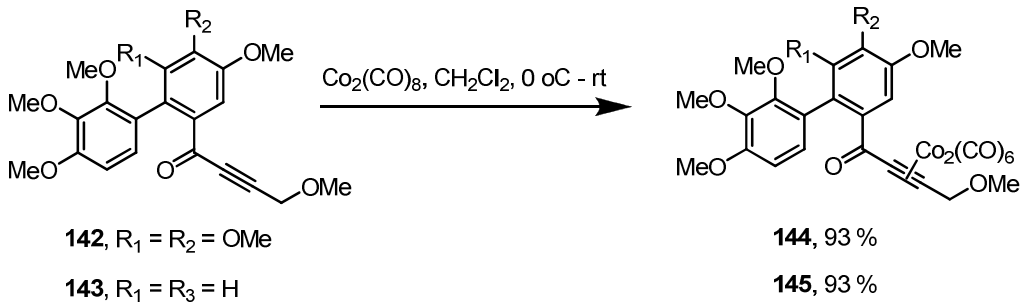


Figure 2.5. *Complexation reaction results for ketone-based synthetic pathway.*

With complexes **(144)** and **(145)** in hand, the stage was set to attempt the intramolecular Nicholas reaction to generate the much desired dibenzocyclooctynedicobalt complexes. Our group has previously utilized EtN^iPr_2 as possible proton scavenging reagent in Nicholas reactions[1], and in some cases this has been effective in affording better product yields. By subjecting complex **(144)** (ca. 4 x 10 mol/L in CH_2Cl_2**)** to reaction with 3 equivalents of BF_3-OEt_2 in presence of 1.5 equivalents of EtN^iPr_2, the dibenzocyclooctynedicobalt complex **(146)** was formed in 61 % yield, although the reaction was quite sluggish (ca. 8 h). Upon attempting the same reaction in absence of EtN^iPr_2, the reaction time decreased significantly, and the yield increased by 20 % (to 85 %). The analogous cyclization reaction of complex **(145)** was also performed in absence of EtN^iPr_2 and afforded cyclized complex **(147)** in excellent yield (81 %) (Figure 2.6). Adding more than 3 equivalents of BF_3-OEt_2 to the reaction mixture had a minor effect on increasing the reaction rate, but had a more negative effect by increasing the rate of decomposition of starting material, and hence decreasing the yield. Employing less than 2 equivalents of BF_3-OEt_2 resulted in reaction being sluggish and an increased reaction time; this in turn affords poorer yield due to decomposition. Hence 3 equivalents was the ideal amount of Lewis acid to be used. Cyclized products **(146)** and **(147)** essentially have the same thermal stability as

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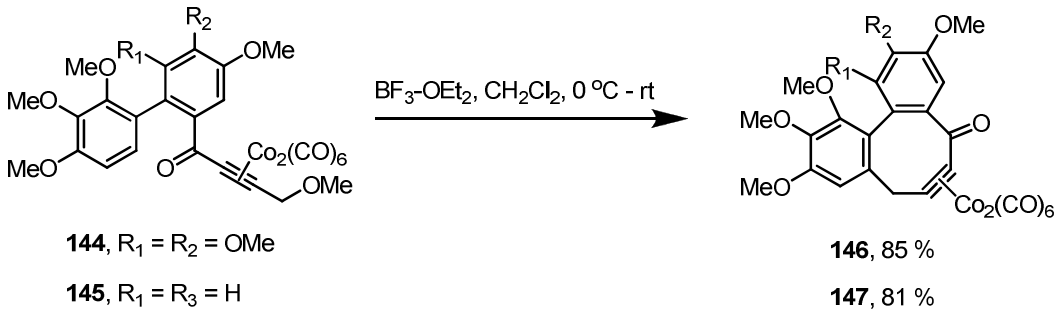
the corresponding starting materials **(144)** and **(145)**, as they were readily purified chromatographically and could be stored at -20 ^{o}C for long periods of time.



144, $R_1 = R_2 = OMe$

145, $R_1 = R_3 = H$

146, 85 %

147, 81 %

Figure 2.6. *Intramolecular Nicholas reaction results for ketone-based synthetic pathway.*

Different derivatives of dibenzocyclooctynedicobalt complexes, namely **(148)**, **(149)**, **(150 a)** and **(150 b)**, similar to **(146)** and **(147)** have been previously synthesized as a requirement for an undergraduate thesis (Figure 2.7).[3] The synthesis of these dibenzocyclooctynedicobalt complexes was executed in the similar synthetic fashion as compounds **(146)** and **(147)** with the exception that $EtN^{i}Pr_2$ was utilized as potential proton scavenger. Compounds **(150a)** and **(150b)** have been acquired from the cyclization of the same acyclic precursor in the same reaction in 10:1 ratio, respectively. These regioisomeric products were inseparable by chromatographic procedures as evident by TLC.

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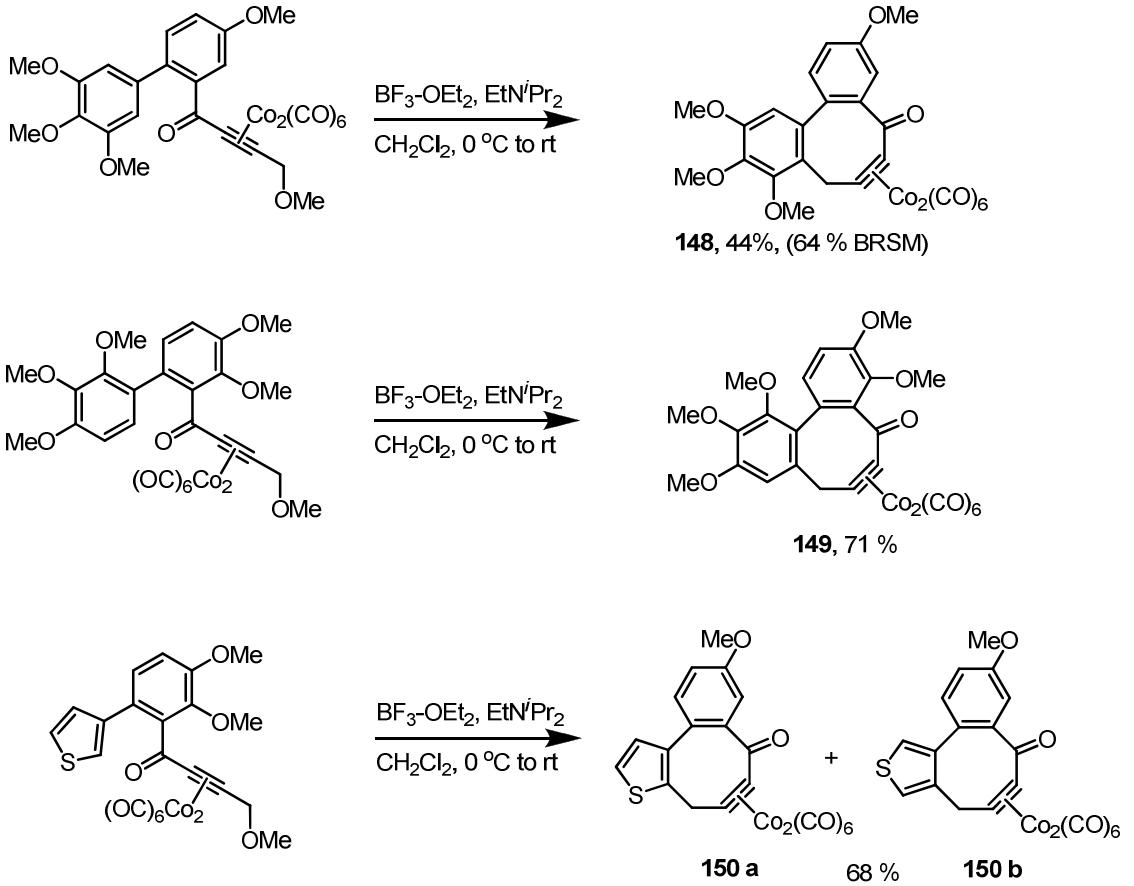

Figure 2.7*. Dibenzocyclooctynedicoablt complexes obtained during undergraduate research.*[3]

With the dibenzocyclooctynedicobalt complexes in hand, the question of decomplexation reactions became critical (Table 2.1). The first choice was to subject complex **(148)** to a reductive decomplexation reaction with triethylsilane and bis(trimethylsilane)acetylene as scavenging alkyne, to produce a triethylvinylsilane intermediate, to which TFA was added with the intent of generating the intended alkene **(151)**. These decomplexation conditions have proven to be very effective for dibenzocycloheptynedicobalt complexes.[1] However, once the reaction was performed on complex **(148)**, complete decomposition of starting material occurred and no product was

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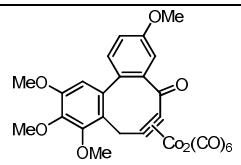
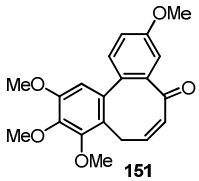
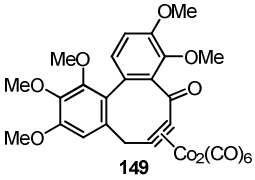
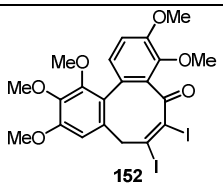
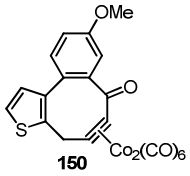
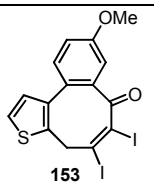
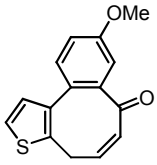
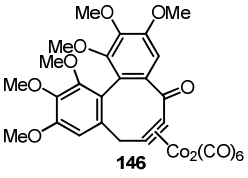
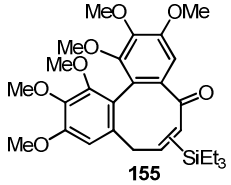
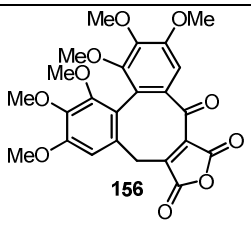
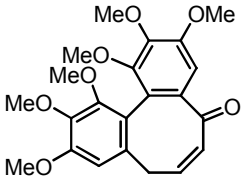
obtained. Complex **(150)** was also subjected to the reaction with triethylsilane and bis(trimethylsilyl)acetylene, and the corresponding triethyvinylsilane intermediate was isolated in 71 % yield. However, once the triethylvinylsilane intermediate is subjected to reaction with CsF in order to remove the triethylsilane adduct, reaction was very sluggish and only produced trace amounts of product **(154)**. Following these results, complexes **(149)** and **(150)** were subjected to decomplexation reactions with I_2 in benzene in hopes to obtain diiodoalkene products **(152)** and **(153)**, respectively. The diiodoalkene would yield a great synthetic handle for further synthesis. However, upon reaction completion compound **(152)** was isolated in only 10 % yield, while compound **(153)** was not detected at all. In both cases starting material decomposes completely and cannot be recovered.

Being closer to dibenzocyclooctadiene target molecules and due to time constraints, focus was shifted to carrying out decomplexation reactions on complex **(146)**. Initially complex **(146)** was subjected to reaction with triethylsilane in presence in of bis(trimethylsilyl)acetylene, and triethylvinylsilane product **(155)** could be isolated in excellent yield (93 %). Unfortunately, trying to remove triethylsilane moiety by reaction with TFA, CsF or TBAF were unsuccessful. Reacting complex **(146)** with CAN in H_2O/acetone media, failed to produce any anhydride product **(156)**[4]. CAN conditions seem to be harsh for the complex and total decomposition of starting material occurred. One set of conditions that were promising involved decomplexation of compound **(146)** by $Na_2H_2PO_4$ at elevated temperature[5]. This reaction afforded intended alkene **(157)** in 43 % yield, along with 13 % of recovered starting material. If the reaction was continued for extended period of time, degradation of product was evident under these conditions.

References start on page 73.

Table 2.1. *Attempts at decomplexation of dibenzocyclooctynedicobalt complexes.*

Starting Material	Decomplexation Conditions	Intended Product	Yield
 **148**	1) Et_3SiH, 1,2-dichloroethane, BTMSA 2) TFA	 **151**	complete decomposition of staring material
 **149**	I_2, benzene	 **152**	10 %
 **150**	I_2, benzene	 **153**	complete decomposition of staring material
	1) Et_3SiH, 1,2-dichloroethane, BTMSA 2) CsF, H_2O/acetone	 **154**	trace
 **146**	Et_3SiH, 1,2-dichloroethane, BTMSA	 **155**	93 %
	CAN, H_2O/acetone	 **156**	complete decomposition of staring material
	Condition 1: H_2O/toluene, reflux Condition 2: $Na_2H_2PO_4$, 2-methoxyethanol, 70 ^oC	 **157**	Condition 1: complete decomposition of staring material Condition 2: 43 % **(157)** 13 % **(146)**

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Complex **(146)** was also subjected to the Bu_3SnH decomplexation reaction (Figure 2.8). To our surprise, over-reduced compound **(158)** was the predominant product (82 % yield), while the intended alkene **(157)** was minor product, obtained in 9 % yield.

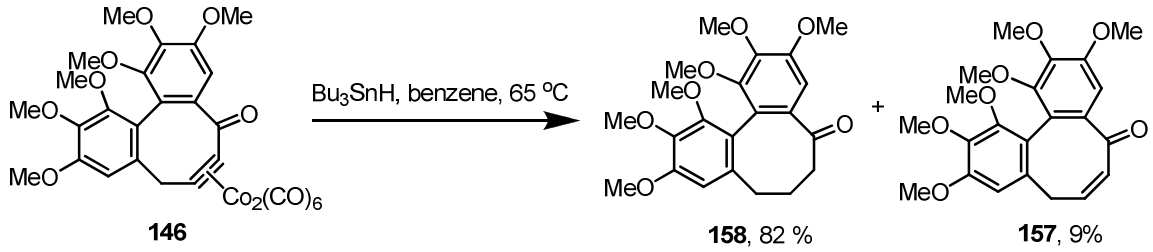
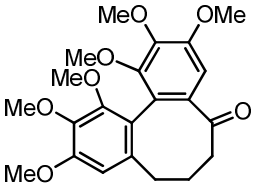
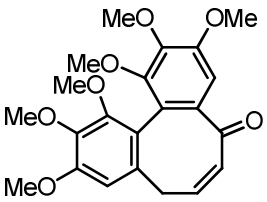


Figure 2.8. *Decomplexation reaction with Bu_3SnH in dibenzocyclooctene synthesis.*

Even though over-reduced compound **(158)** was not the intended alkene, the possibility existed that it could be transformed into the desired alkene **(157)**[6-9]. Several different known dehydrogenation reactions were attempted (Table 2.2) with the intent of obtaining the alkene **(157)**. Interestingly, none of the conditions outlined (Table 2.2) were effective in generation of intended product. In most of the cases starting material was recovered as **(158)** seems to be very unreactive to the standard sets of the conditions applied.

Table 2.2. *Attempts at dehydrogenation of dibenzocyclooctanone **(158)**.*

Starting material	Reaction conditions	Product	Yield
 **158**	IBX, NMO, DMSO, 60 °C	 **157**	No reaction (recovered **127**)
	PhSeCl, EtOAc, rt		No reaction (recovered **127**)
	LDA, TMSCl, 0 °C to rt $Pd(OAc)_2$, CH_3CN, rt		Trace
	$PhSO_2Me$, KH, THF, reflux		No reaction (recovered **127**)

In order to expand the scope of the cyclization reactions a second synthetic pathway towards the synthesis of dibenzocyclooctynedicobalt complexes was investigated

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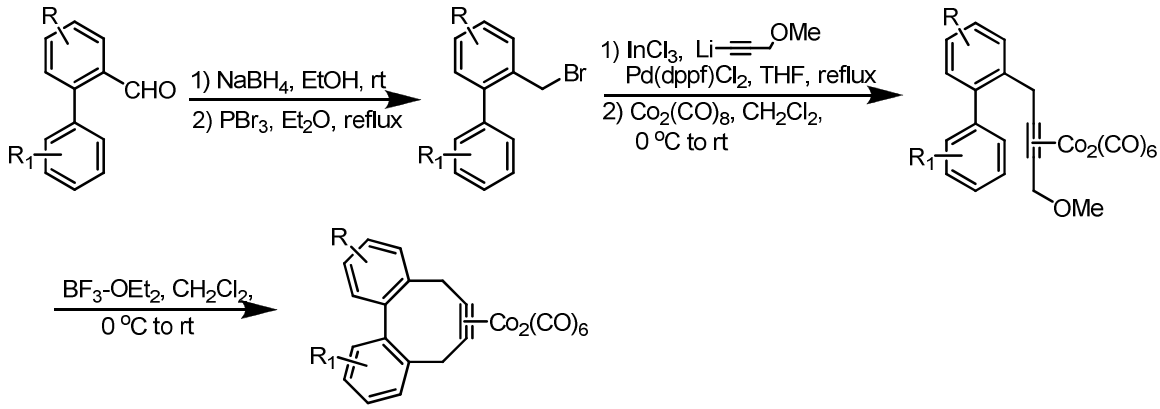
(Scheme 3). This particular synthetic pathway was designed to ultimately yield dibenzocyclooctynedicobalt complexes with no substitution at the position adjacent to the hexacarbonylalkynedicobalt moiety.



Scheme 2.3. *Second synthetic pathway for synthesis of dibenzocyclooctynedicobalt complexes.*

Starting with the previously discussed biarylcarbaldehydes **(133)** – **(136)**, reduction of the aldehyde was carried out by $NaBH_4$ in anhydrous ethanol. The reduction proceeded quite smoothly and products **(159)**, **(160)**, **(161)** and **(162)** were isolated in excellent yields (Figure 2.9). After reaction completion the products were almost perfectly pure after the standard workup procedure. However, in order to take greater care, the compounds were still chromatographically purified.

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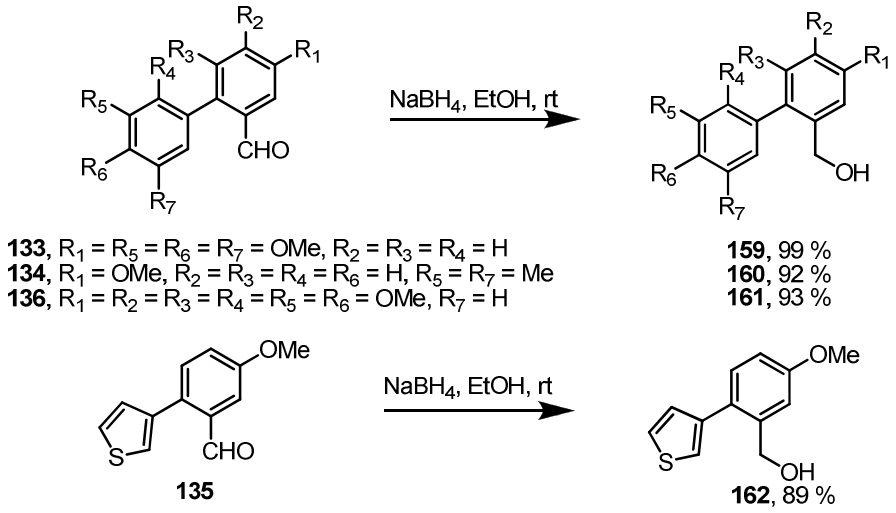

Figure 2.9. *Aldehyde reduction results in dibenzocyclooctane precursor synthesis.*

With the alcohols **(159)** – **(162)** in hand, a substitution reaction was carried out using PBr_3, to generate the benzylic bromide adducts **(163)** – **(166)**, respectively (Figure 2.10). The reactions were carried out at slightly elevated temperatures and products were isolated in moderate to excellent yields.

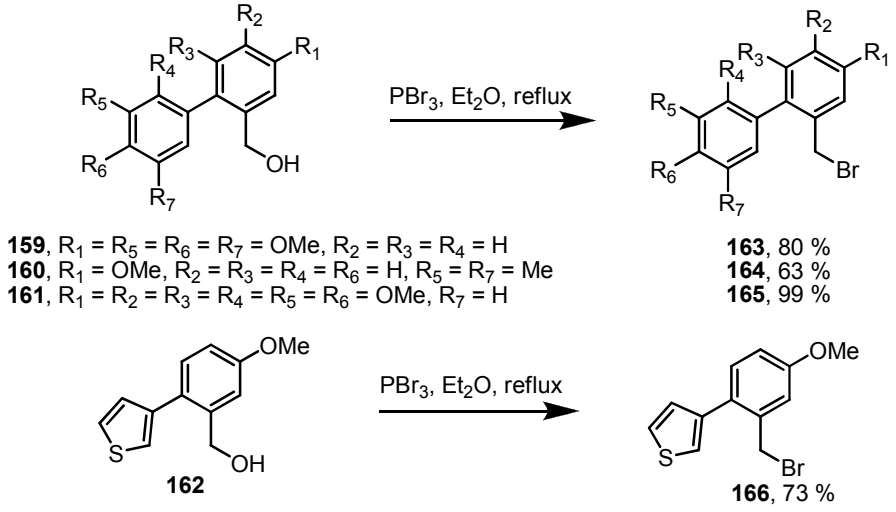

Figure 2.10. *Bromination reaction results in dibenzocyclooctane precursor synthesis.*

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The benzyl bromide adducts gave a great synthetic handle for the installation of the necessary propargyl ether unit for complexation and cyclization reactions. The first attempt at synthesis of benzyl propargyl ether species consisted of subjecting benzyl bromide **(163)** simply to the reaction with lithiated propargyl ether with the expectation that **(167)** could be generated by a simple S_N2 substitution. After completion, it was evident that reaction was indeed successful and compound **(167)** was isolated in 61 % yield.

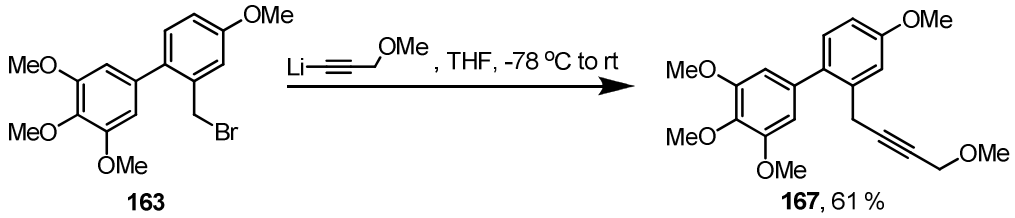

Figure 2.11. *Result for formation of benzyl propargyl ether by S_N2 substitution.*

This initial result led to the expectation that benzyl bromides **(164)** – **(166)** would undergo the same transformation under the same set of conditions to generate corresponding benzyl propargyl ethers. However, to our surprise, once compounds **(164)** – **(166)** were subjected to the same set of conditions as compound **(163)** the reactions were very sluggish and afforded the corresponding benzyl propargyl ether products in very poor or no yields. In view of this, resort was made to attempts at copper mediated coupling reactions of propargyl ether with benzyl bromides **(164)** – **(166)**. The CuI promoted Wullf procedure[10] and CuBr mediated coupling[11] were also unsuccessful at generating the intended benzyl propargyl ether product. In both cases, the starting materials were completely recovered. Fortunately when benzyl bromides **(164)** – **(166)** were subjected to palladium catalyzed coupling reactions with trialkynylindium species, as demonstrated by Sarandeses and coworkers[12], the corresponding benzyl propargyl ether products **(168)** – **(170)** were obtained in moderate yields (Figure

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2.12). Analogous to this reaction, compound **(164)** was subjected to a palladium catalyzed reaction with the corresponding bromo(alkynyl)zinc, as demonstrated by Negishi and coworkers[13], and the corresponding product **(168)** was isolated in 57 % yield.

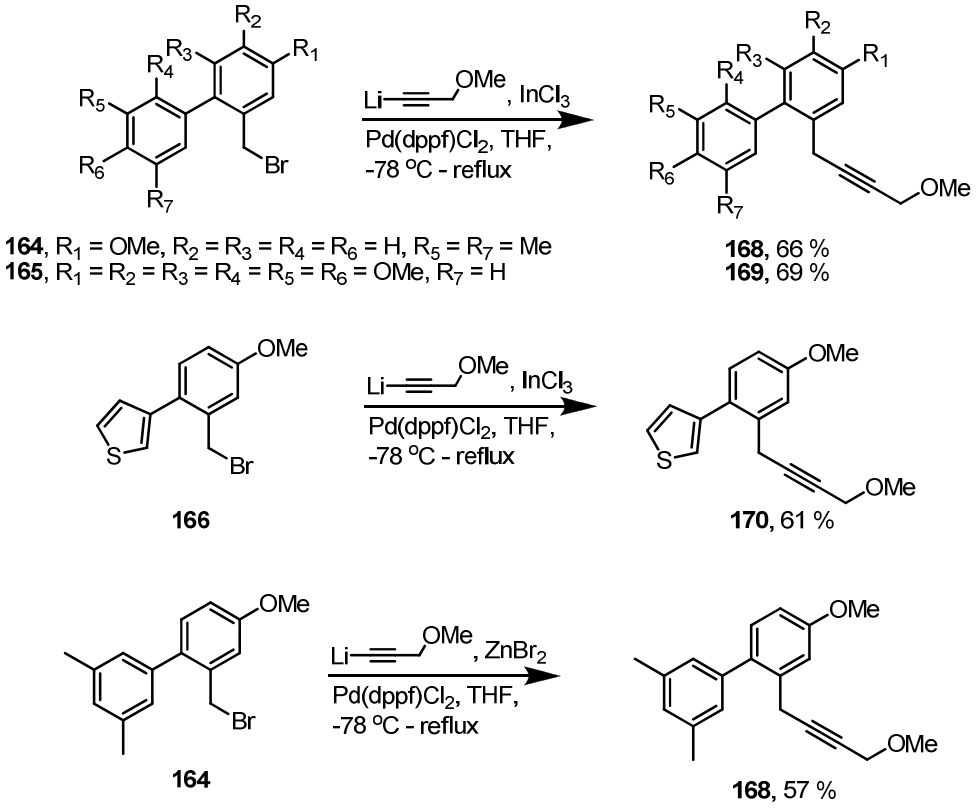

Figure 2.12. *Results for palladium catalyzed trialkynylindium and bromo(alkyny)zinc coupling with benzyl bromides.*

Upon obtaining benzyl propargyl ethers **(167)** – **(170)**, complexation reactions were performed in the presence of excess $Co_2(CO)_8$, and the corresponding hexacarbonylalkynedicobalt complexes **(171)** – **(174)** were obtained in excellent yields (Figure 2.13). Following complexation of the alkyne onto the dicobalt unit, there is an evident color change from colorless viscous liquid or powder to dark red oil or dark red solid. Another noteworthy effect of complexation was the downfield shift of signals corresponding

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to two adjacent CH_2 groups in proton NMR spectra. These complexes exhibit almost identical properties as those described for complexes **(144)** and **(145)**. Good air and thermal stability of these complexes allowed them to be easily purified by column chromatography and stored at - 20 ^{o}C for extended periods of time. These compounds were also stable at room temperature in a variety of organic solvents under an atmosphere of nitrogen.

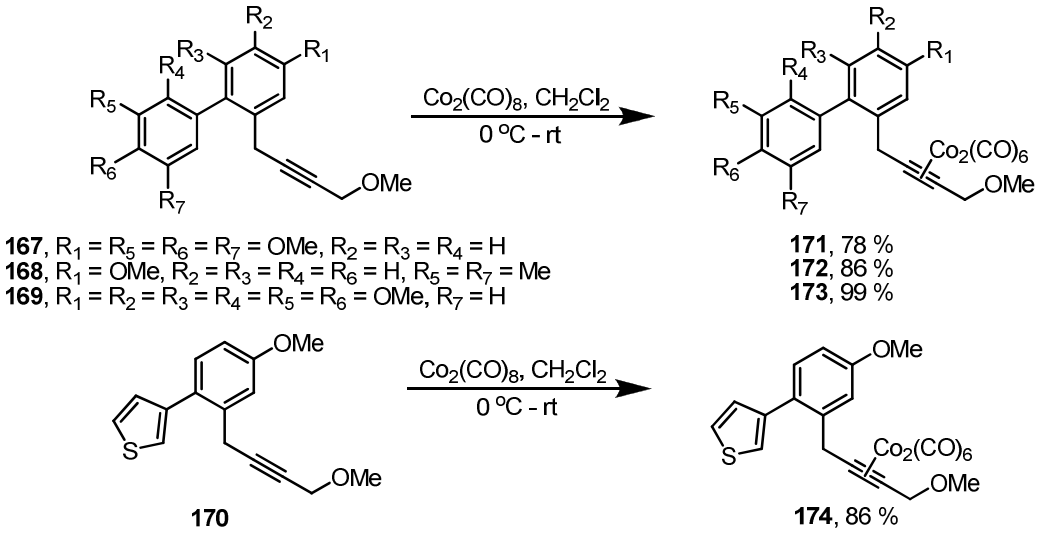

Figure 2.13. *Complexation reaction results for second synthetic pathway in dibenzocyclooctane synthesis.*

By subjecting complexes **(171)** – **(174)** to BF_3-OEt_2 mediated cyclization reactions under conditions analogous to **(144)** and **(145)**, dibenzocyclooctynedicobalt complexes **(175)** – **(178)** could be generated in excellent yields (Figure 2.14). The reaction concentration for every cyclization was adjusted to be 4 x 10^{-4} mol/L in order to minimize possibility of intermolecular reactions. The rates of the cyclization reaction of complexes **(171)** – **(174)** were approximately 3 fold faster than that of their ketone bearing analogues **(144)** and **(145)**. The cyclization of complex **(174)** produced a single C-2 substitution regioisomer, as evident by ^{1}H and ^{13}C NMR spectroscopy. Unlike cyclization of dibenzocycloheptynes,[1] where the

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presence of EtN^iPr_2 had a positive impact on increasing the yield of the reaction, in this case presence of EtN^iPr_2 significantly slowed the reaction time and therefore hindered product formation; this was also analogous to the cyclization reactions involving complexes **(144)** and **(145)**.

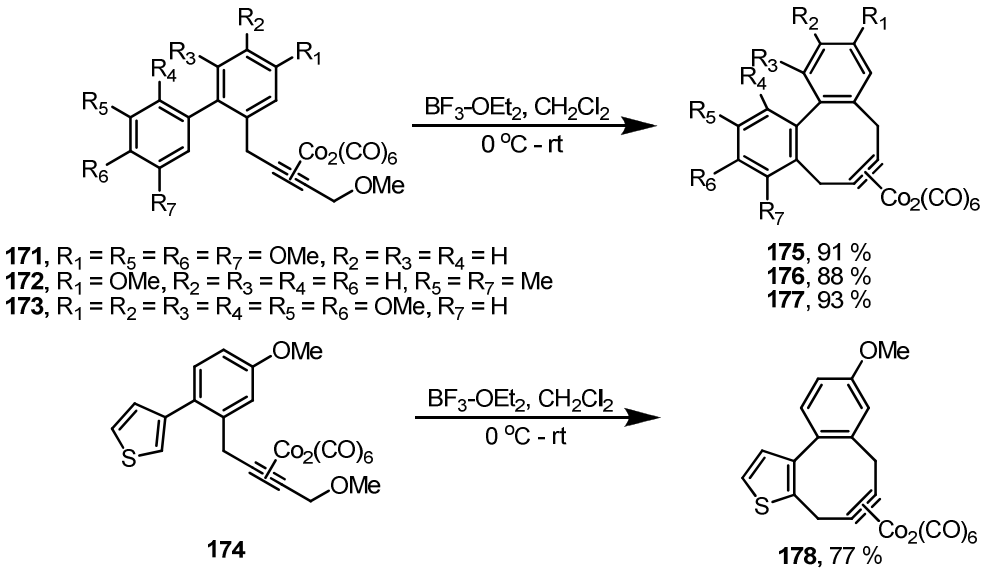

Figure 2.14. *Intramolecular Nicholas reaction results for second synthetic pathway in dibenzocyclooctyne synthesis..*

With dibenzocyclooctynedicobalt complex **(177)** in hand the reductive decomplexation protocols were attempted, with the intent of obtaining the corresponding alkene **(180)**. When complex **(177)** was subjected to the decomplexation reaction mediated by the Et_3SiH in presence of bis(trimethylsilyl)acetylene at elevated temperature, triethylvinylsilane intermediate **(179)** was obtained. Rather than complete purification, the decomposition by products were simply removed by filtration through a plug of silica, with subsequent solvent removal. Once the residue containing triethylvinylsilane intermediate **(179)** was subjected to reaction with TFA, we were pleased to find that the corresponding alkene **(180)** was obtained in 97 % isolated yield for the two steps. This decomplexation

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reaction played a crucial part in the synthesis, as it provided a necessary alkene which ultimately will afford the target molecules **(183)** and scizandrin A **(186)**, as demonstrated later in the chapter.

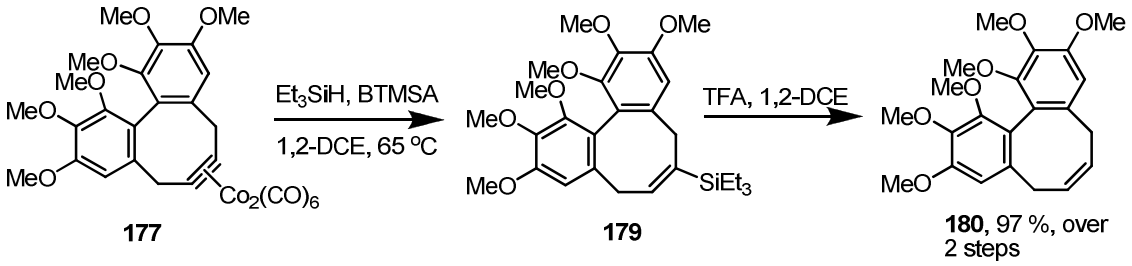

Figure 2.15. *Reductive decomplexation of dibenzocyclooctynedicobalt complex.*

Dibenzocyclooctyne **(180)** was initially subjected to the reaction with m-CPBA in hopes to synthesize epoxide **(181)**. The epoxide **(181)** was indeed generated, but with maximum yield of 59 %. In order to improve on the epoxidation yield, compound **(180)** was subjected to reaction with freshly prepared dimethyldioxirane[14]. Upon reaction completion, intended epoxide product **(181)** was obtained in much better yield of 87 % (Figure 2.16). The epoxidation of the alkene occurred on a single face and with the expected *cis*- diastereomer as the predominant product in this case, as evident by ^{1}H NMR spectroscopy.

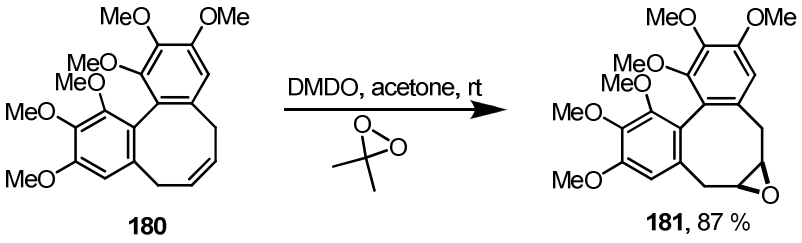

Figure 2.16. *Epoxidation result in dibenzocyclooctane synthesis.*

In order to ring open the epoxide **(181)** and install a methyl group, epoxide **(181)** was reacted with MeLi in presence of CuI, with the expectation that the epoxide would undergo nucleophilic ring opening to generate alcohol **(182)**. Disappointingly, no product was isolated

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and only 50 % of the starting epoxide was recovered. Fortunately, it is well known in the literature that in some instances Lewis acids can promote epoxide ring opening by nucleophiles.[15] When the epoxide **(181)** was subjected to reaction with lithium dimethyl cuprate in the presence of BF_3-OEt_2, the intended alcohol **(182)** was generated in 92 % isolated yield (Figure 2.17). This process required careful experimentation; due to poor solubility of epoxide **(181)** in diethyl ether, it had to been dissolved in toluene and added to solution of Me_2CuLi in diethyl ether. To this reaction mixture was then added the BF_3-OEt_2. The evidence of the relative stereochemistry is apparent in ^{1}H NMR spectra.

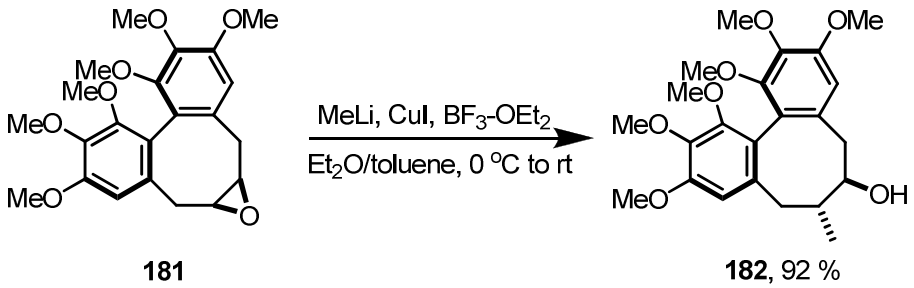

Figure 2.17. *Me_2CuLi mediated epoxide ring opening in isoschizandrin syntheis.*

Swern oxidation of alcohol **(182)** afforded the corresponding ketone **(183)** in excellent yield (95 %) (Figure 2.18). Compound **(183)** is known, and has previously been converted to both isochizandrin and schizandrin[16]; hence formal total synthesis at this point has been achieved.

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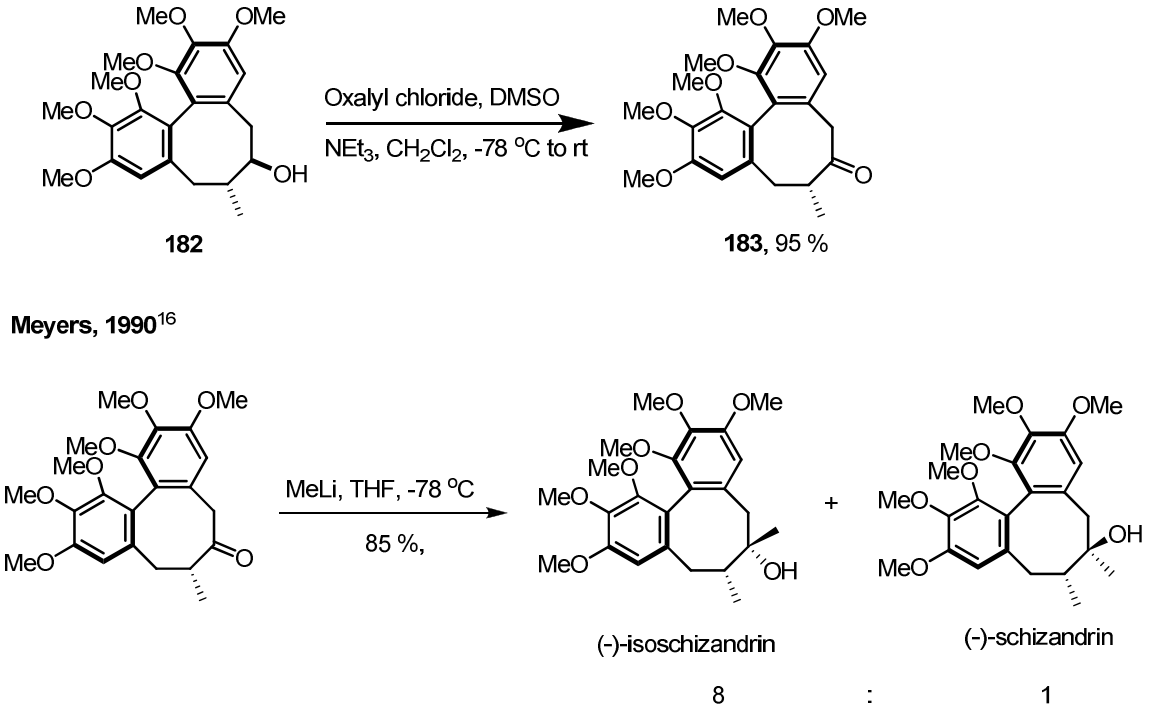

Figure 2.18. *Oxidation of alcohol and formal synthesis of isoschizandrin and schizandrin.*

While we have completed the synthesis of desired compound **(183)**, the attention was shifted to secondary goal, which was exploring if compound **(183)** could be converted to schizandrin A. Initially, ketone **(183)** was subjected to the Wittig reaction with methyltriphenylphosphonium bromide and potassium *tert*-butoxide as a base. This reaction did not proceed with the retention of stereochemistry at the carbon centre α- to the ketone, as base induced epimerization had occurred, and exo-methylene products **(184)** and **(185)** were obtained in 91 % yield as a 50 : 50 mixture of inseparable diastereomers (Figure 2.19) as evident by ^{1}H NMR spectra. Both olefins **(184)** and **(185)** were previously synthesized by Meyers and coworkers[16], and hence ^{1}H NMR and ^{13}C NMR spectra were compared for relative stereochemical analysis.

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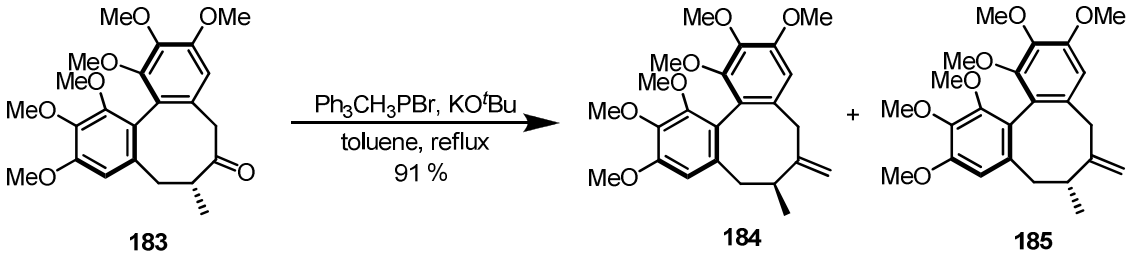

Figure 2.19. *Wittig reaction result in schizandrin A syntheis.*

Realizing this, an alternative alkylidenation methodology, developed by Yan and coworkers[17], was employed to achieve the synthesis of single isomer of exo-methylene **(185)**. Hence, subjecting ketone **(183)** to direct methylenation with CH_2Cl_2, promoted by $Mg/TiCl_4/THF$, gave intended exo-methylene product **(185)** as a single diastereomer in 77 % yield (Figure 2.20), as evident by ^1H NMR spectroscopy[16].

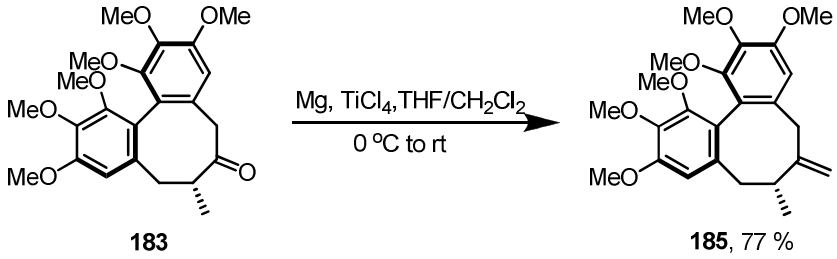

Figure 2.20. *Direct methylenation of ketone with dichloromethane in schizandrin A synthesis.*

When a 50 : 50 mixture of exo-methylene compounds **(185)** and **(184)** underwent a hydrogenation reaction with H_2 on Pd/C, an isomeric mixture consisting of schizandrin A **(186)**, compound **(187)** and compound **(188)** was isolated in 90 % yield in 8 : 6.5 : 1 ratio, respectively (Figure 21). However, when single diatereomer **(185)** is subjected to the same hydrogenation reaction conditions, isomeric mixture of schizandrin A **(186)**, compound **(187)** and compound **(188)** is once again isolated in 94 % yield, but with ratio of 8 : 15 : 1, respectively (Figure 2.21). Diastereomers **(186)**, **(187)**, and **(188)** are inseparable and their

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presence was evident by ^{1}H and ^{13}C NMR spectroscopy. Due to the time constraints, further methods for the synthesis of diastereomerically pure schizandrin A were not explored.

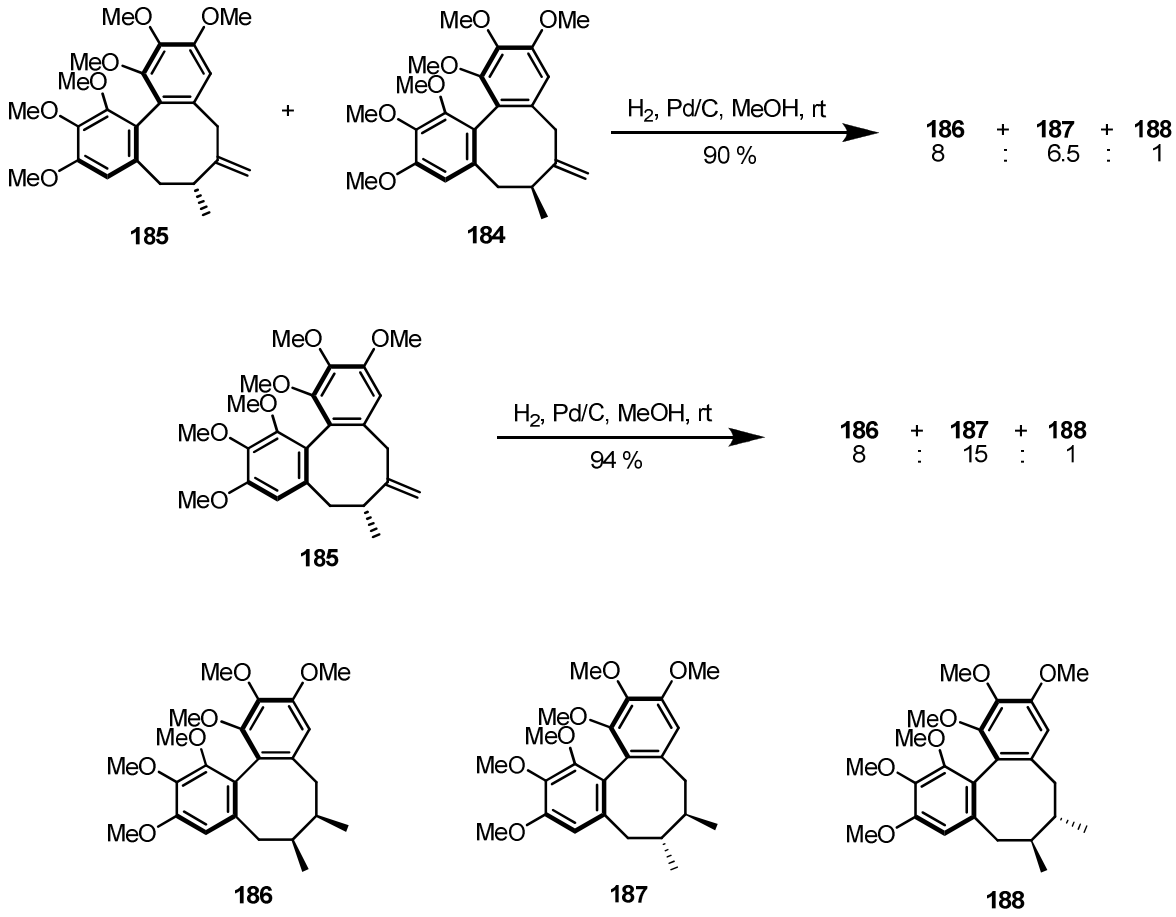

Figure 2.21. *Hydrogenation of exo-methylene cyclooctenes and racemic synthesis of schizandin A as observed by 1H NMR spectroscopy.*

2.2 Tenuifolin synthesis by Nicholas reaction chemistry

Given the group's expertise dibenzocycloheptynedicobalt chemistry, a strategy for the synthesis of tenuifolin has been devised, analogous to that for the synthesis of allocolchicine NSC 51046 and of (-)-allocolchicine[1]. We have envisioned synthesis of

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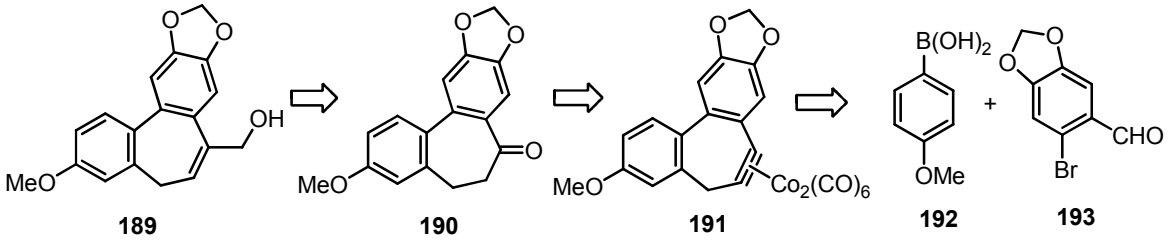
tenuifolin **(189)** proceeding through the ketone compound **(190)**, which should be accessible from the dibenzocycloheptynedicobalt complex **(191)** (Scheme 2.4), as demonstrated by our previous research. To arrive at the complex **(191)** a biaryl system produced from cross-coupling reaction of 4-methoxyphenylboronic acid **(192)** and 6-bromo-1,3-benzodioxole-5-carboxaldehyde **(193)** was planned.



Scheme 2.4. *Retrosynthetic approach towards synthesis of tenuifolin (159).*

As expected, the Suzuki cross-coupling reaction of 4-methoxyphenylboronic acid **(192)** and 6-bromo-1,3-benzodioxole-5-carboxaldehyde **(193)** proceeded quite smoothly and afforded the intended biaryl product **(194)** in good yield (80 %) (Figure 2.22). With the biaryl aldehyde **(194)** in hand, it was ready to be subjected to Corey-Fuchs conditions in order to produce corresponding propargyl alcohol moiety.

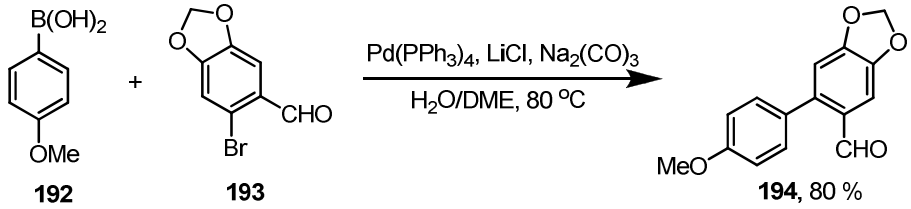


Figure 2.22. *Suzuki cross-coupling result in tenuifolin synthesis.*

Reaction of biaryl aldehyde **(194)** with carbon tetrabromide and triphenylphosphine, initially produced the dibromoalkene intermediate **(195)**, as evidenced by ^{1}H NMR spectroscopy. This intermediate is very stable and high yielding. For purposes of this

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synthesis the reaction mixture was simply filtered through the plug of silica in order to remove the phosphonium salts present in the mixture, with the unpurified dibromoalkene intermediate **(195)** exposed to next step of reaction. Subjecting this dibromoalkene to reaction with *n*-BuLi (2.1 eqiv.) followed by the addition of paraformaldehyde at low temperature produced the intended propargyl alcohol product **(196)** in good yield (86 %) over two steps (Figure 2.23). Due to the high moisture sensitivity of the organolithiums, second part of this reaction was carried out with extreme care.

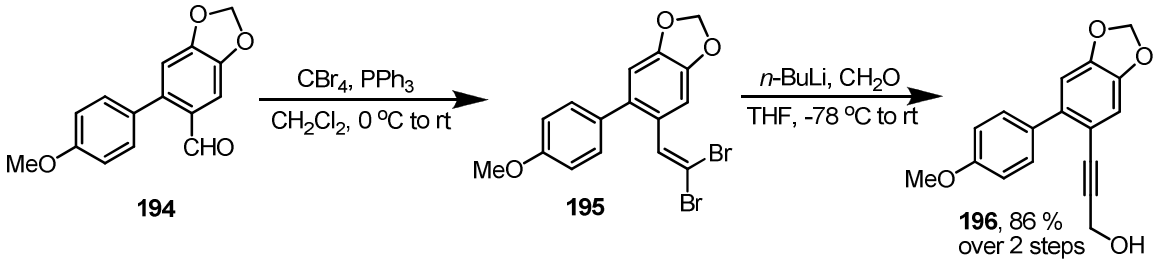

Figure 2.23. *Corey-Fuchs result in tenuifolin synthesis.*

Before complexation of the alkyne **(196)** with dicobalt octacarbonyl, it was preferable to convert the alcohol functional group to the corresponding acetate. This was performed by subjecting alcohol **(196)** to reaction with pyridine and acetic anhydride. The reaction progress was monitored by means of TLC and upon completion, the excess pyridine and acetic anhydride were simply removed under reduced pressure and the product was taken on to the next step. Complexation of the propargyl acetate then afforded the intended complex **(197)** in 85 % yield over the two steps (Figure 2.24).

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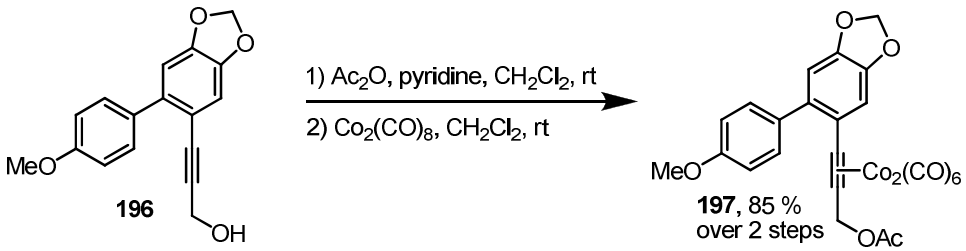

Figure 2.24. *Complexation result in synthesis of tenuifolin.*

When complex **(197)** was subjected to a cyclization reaction attempt with BF_3-OEt_2 without the presence of EtN^iPr_2, a reaction proceeded to give dibenzocycloheptynedicobalt complex **(191)**. However, the reaction rate was sluggish and over an extended period of time (ca. 6 h) produced uidentified side products evident by TLC. The maximum yield obtained under these conditions was 61 %. Upon addition of EtN^iPr_2 to the reaction, the rate of cyclization slightly decreased, however, the yield had increased to 72 % (Figure 2.25). This rate of cyclization reaction was much slower (ca. 6 h) when compared to any dibenzocycloheptynedicobalt derivatives synthesized previously by our group[1].

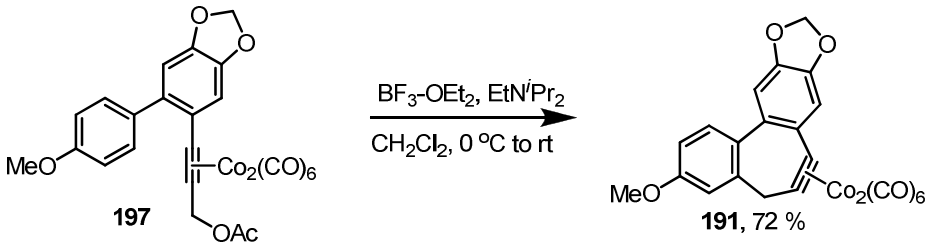

Figure 2.25. *Intramolecular Nicholas reaction result in synthesis of tenuifolin.*

Reductive decomplexation of dibenzocycloheptynedicobalt complex **(191)**, by means of the two step procedure involving Et_3SiH, BTMSA and TFA, produced the intended alkene **(198)** in 76 % yield (Figure 2.26). Once again the intermediate triethylvinylsilane was simply filtered through a plug of silica to remove gross decomposition by product, but not completely purified.

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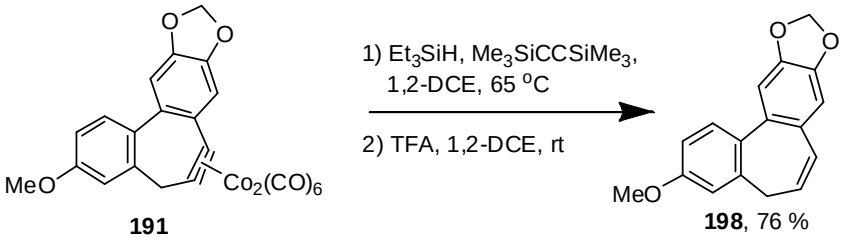

Figure 2.26. *Reductive decomplexation reaction result in tenuifolin synthesis.*

As expected, the standard hydroboration/oxidation protocols formed the corresponding alcohol. Without complete purification, the alcohol was subjected to a Swern oxidation reaction to produce the intended ketone **(190)** in 76 % yield over the two steps (Figure 2.27).

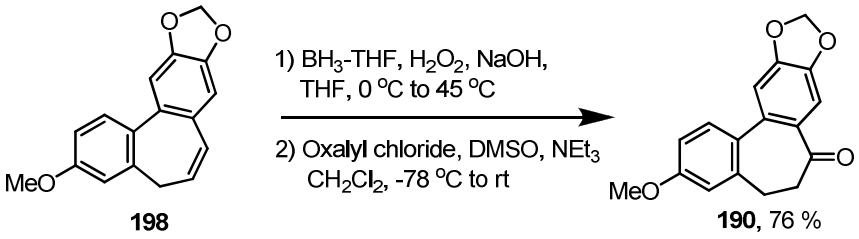

Figure 2.27. *Hydroboration and oxidation in tenuifolin synthesis.*

With the ketone **(190)** in hand, our initial thoughts were to utilize a Shapiro reaction[18,19], which is a *n*-BuLi mediated tosylhydrazone decomposition reaction to produce vinyllithium intermediate, which can be trapped with paraformaldehyde to rapidly produce corresponding alcohol and hence tenuifolin **(189)**. By monitoring the reaction progress with NMR, it was determined determined that ketone **(190)** was successfully converted to tosylhydrazone intermediate **(199)** by reaction with p-toluenesulfonyl hydrazide; this intermediate **(199)** was further used without purification (Figure 2.28). However, when the tosylhydrazone intermediate **(199)** was subjected to reaction with *n*-BuLi (2 equiv) followed

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by addition of paraformaldehyde, to our disappointment no intended product was generated and complete decomposition of starting material took place.

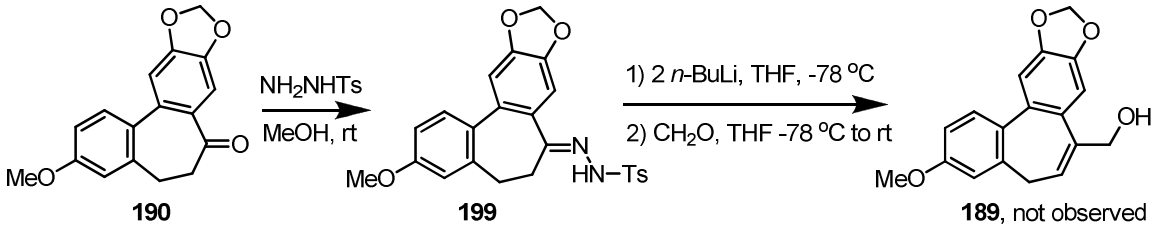

Figure 2.28. *Shapiro reaction in tenuifolin synthesis.*

This unexpected result forced a revision in the strategy of accessing tenuifolin **(189)** from the ketone **(190)**. There was no difficulty in reacting ketone **(190)** with methyltriphenylphosphonium bromide in presence of potassium *tert*-butoxide to generate exo-methylene product **(200)** (70 % yield). This exo-methylene compound **(120)** was subjected to an epoxidation reaction with freshly prepared DMDO[14], and intended epoxide **(201)** was in isolated in 72 % yield (Figure 2.29). Epoxidation of compound **(200)** was also attempted with m-CPBA, but reaction did not yield any product and starting material **(200)** was not recovered.

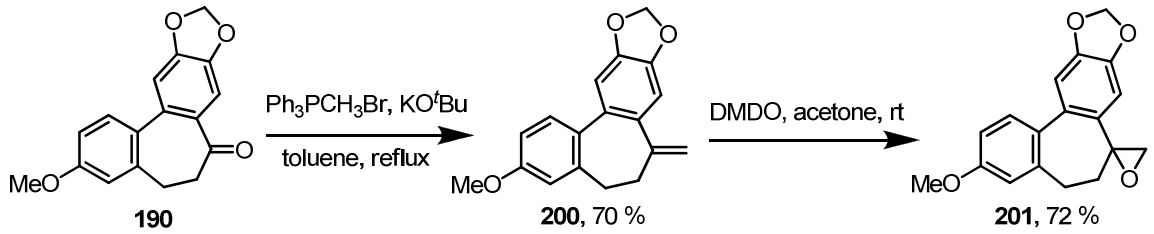

Figure 2.29. *Wittig and epoxidation reaction results in tenuifolin synthesis.*

By subjecting epoxide **(201)** to the ZnI_2 mediated ring opening reaction, a methodology developed by Campbell and coworkers[20], it was possible to obtain tenuifolin. However, the reaction afforded tanuifolin **(189)** in only 19 % yield, along with unidentified

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side products (Figure 2.30). Due to the time constraints, further optimization of epoxide **(201)** opening reaction was not explored.

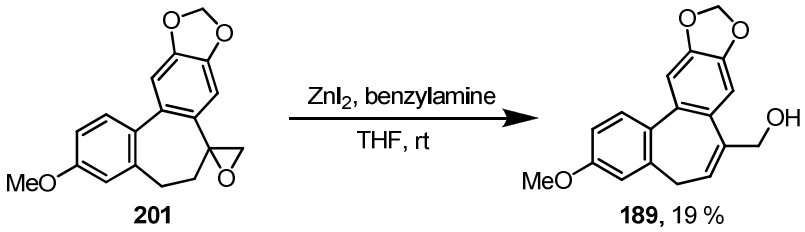

Figure 2.30. *ZnI_2 mediated epoxide ring opening in tenuifolin synthesis.*

Nevertheless, this completes the second total synthesis of tenuifolin, and demonstrated the ability of intramolecular Nicholas reaction chemistry at getting rapid accsess to dibenzocycloheptane natural products.

2.3 Conclusion

Following the investigations we have determined that dibenzocyclooctadiene complexes can be formed readily by intramolecular Nicholas reaction where BF_3-OEt_2 is used as a Lewis acid. Cyclized compounds **(146)**, **(147)**, and **(175)-(178)** were prepared in good to excellent yield when $4x10^{-3}$ mol/L concentration of starting material was used. Upon cyclization of thiophene complex **(174)** it was evident by ^1H and ^{13}C NMR spectroscopy that single isomer is formed. In addition to this, cyclized complex **(178)** was proven to be a great synthetic precursor towards formal synthesis of (±)-isoschizandrin, as well as mixture of diastereomers that includes schizandrin A.

The investigations into synthesis of tenuifolin by intramolecular Nicholas reaction have provided desirable results. The cyclization reaction of acyclic precursor complex **(197)** has yielded intended dibenzocycloheptynedicobalt compolex **(191)** in good yield. After

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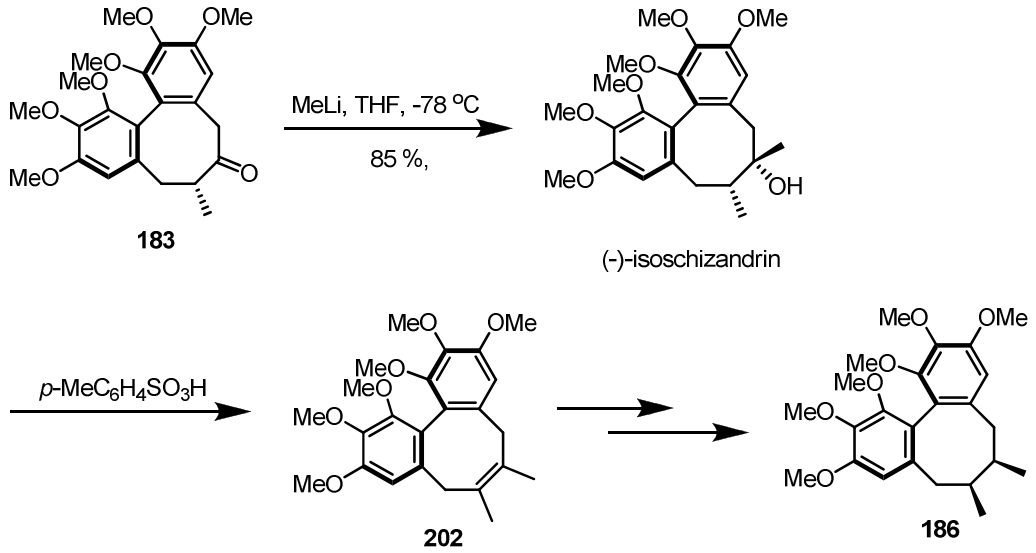
several synthetic steps including: decomplexation, oxidation, Wittig reaction, epoxidation and epoxide ring opening, gave rise to desired target molecule tenuifolin.

2.4 Future work

Question of diastereoselective hydrogenation of exomethylene **(185)** becomes unavoidable as the previous hydrogenation gave rise to mixture of diasteromers **(186)**, **(187)** and **(188)**. Strategy should be devised to exclusively generate diastereomer **(186)** (schizandrin A). An alternative route to accessing diastereomer **(186)** (schizandrin A) could be theoretically achieved through (±)-isoschizandrin itself, which can be acsessesd by reaction of compound **(183)** with MeLi as demonstated by Meyers[16] (Scheme 2.5). Compound (-)-isoschizandrin could then undergo a dehydration reaction to produce compound **(202)**, which could potentially undergo diastereoselective hydrogenation, to yield intended diastereomer **(186)**.



Scheme 2.5. *Alternative route to schizandrin A.*

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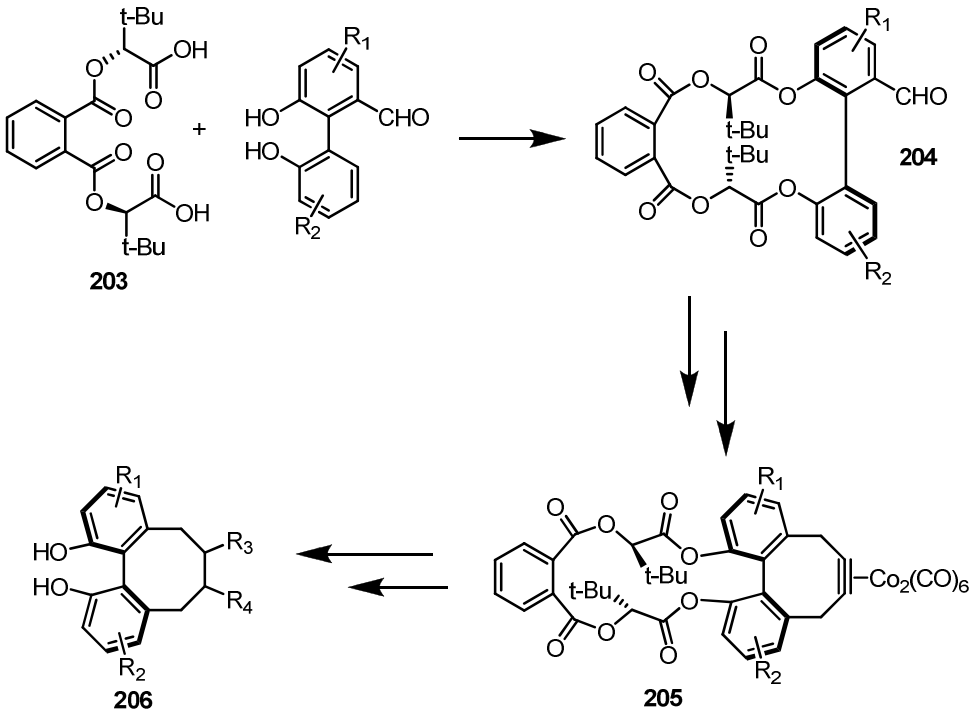
Because naturally occurring dibenzocycloocadienes are isolated as a single atropisomer, it would be ideal to investigate ways to form this single enantiomeric form. Recently, Keay and coworkers have utilized tartaric and butanoic acid derived chiral auxiliaries to achieve several synthesis of biphenyl systems with high diastereoselectivity[21]. Our intent is to apply a similar principle by initially performing Suzuki coupling, placing the chiral auxiliary adduct **(203)** on the molecule which should force one rotamer of **(204)** to be preferred (Scheme 2.6). Following this, cycization would be carried out and once a single diastereomer **(205)** would be constructed, auxiliary group would be removed to afford intended product as a single enantiomer **(206)**. If this process turns out to not be highly selective, the diastereomers should be separable, and single enantiomer could be obtained after hydrolysis.



Scheme 2.6. *Approach to single atropisomer of dibenzocyclooctanes.*

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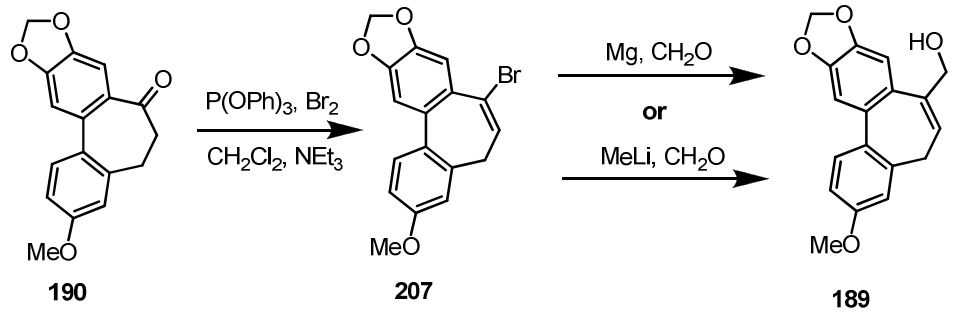
With the tenuifolin **(189)** in hand, optimization of epoxide **(201)** ring opening should be attempted. It would also be wise to revisit the idea of accessing tenuifolin **(189)** through Shapiro reaction from compound **(190)**. Since it was evident by ^{1}H NMR spectroscopy that tosylhydrazone intermediate **(199)** was formed, perhaps optimizing the conditions of tosylhydrazone decomposition by the base would afford the intended tenuifolin **(189)**, and perhaps in better yield than provided by epoxide ring opening.

Improvement on transformation of ketone **(190)** to the tenuifolin **(189)** could be perhaps done through vinyl halide formation. By subjecting ketone **(190)** to the reaction with $P(OPh)_3$ in presence of Br_2, it could be possible to generate vinyl bromide **(207)**, as demonstrated by Prati and co-workers (Figure 2.31).[22] Subjecting vinyl bromide **(207)** to lithium halogen-exchange followed by reaction with paraformaldehyde could afford intended tenuifolin **(189)**. Analogous to this, vinyl bromide **(207)** could undergo reaction with magnesium to generate vinyl-magnesium bromide intermediate, which could be transformed to tenuifolin **(189)** by exposure to paraformaldehyde.



190 **207** **189**

Figure 2.31. Access to tenuifolin through vinyl bromide **(207)**.

By synthesizing tenuifolin **(189)**, the pathway has been opened for the synthesis of reticuol **(208)** or subamol **(209)**. Ideally, demethylation of the methoxy functional group could be executed by conditions outlined on simple systems by Duan and co-workers[23] to

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yield the corresponding alcohol which would afford reticuol **(208)**, and subamol **(209)** should also be accessible by deprotection of methylendioxy moiety to afford the corresponding, diol as demonstrated on simple systems by Wright and co-workers[24] (Figure 2.32).

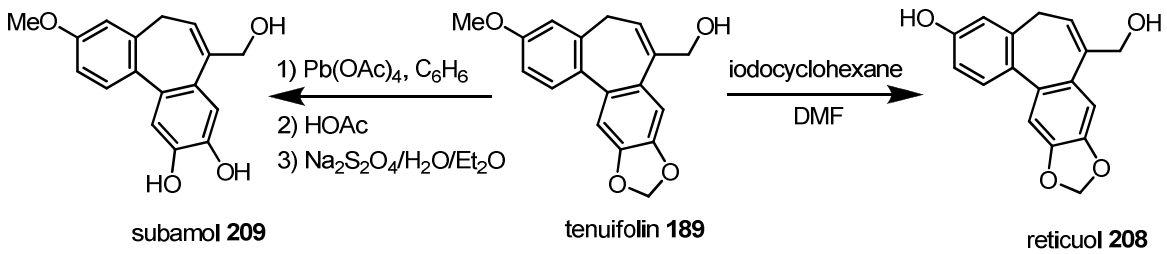

Figure 2.32. *Potential routes to reticuol and subamol from tenuifolin.*

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2.5 References

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CHAPTER 3 : EXPERIMENTAL

3.1 General Methods

Most of the starting materials and reagents that were utilized in the reactions were all purchased from Sigma-Aldrich, with the exception of dicobalt octacarbonyl, which was purchased from Strem chemicals. The starting materials that were purchased were used without further purification unless otherwise described. The reagents BF_3-OEt_2 and $TiCl_4$ were distilled and stored under inert-atmosphere prior to use. Purification of new compounds was carried out by column chromatography, preparative TLC, or by radial chromatography. The silica gel that was used in column chromatography (SilaFlash® P60, 230 – 400 mesh) and preparative TLC (thickness: 1000 μm, indicator: F-254) were purchased from Silicycle Inc. All of the solvents mentioned in preceding reactions (except for DME and 1,2-dichloroethane) were obtained from a solvent purification system (Innovative Technologies), and were used without further drying.

IR spectra listed in the characterization of compounds indicate the absorption peaks with the greatest functional group relevance, with units of cm^{-1}. ^1H NMR data is listed with units of ppm for the peak position and Hz for the coupling constants. Symbols that indicate peak appearance are as following: s – singlet, d – doublet, t – triplet, dd – doublet of doublets, q-quartet. ^{13}C NMR data listed below is in units of ppm. All of the NMR analysis was performed on 300 MHz and 500 MHz Bruker Avance spectrometers at room temperature, as solutions of $CDCl_3$, with 7.27 ppm (residual $CHCl_3$) and 77.0 ppm as the reference chemical shifts for ^1H NMR and ^{13}C NMR spectra, respectively. High Resolution Mass Spectrometry (HRMS) results were obtained by means of Direct Insertion Probe - Electron Ionization method, on a Waters/Micromass GC-ToF Mass Spectrometer performed

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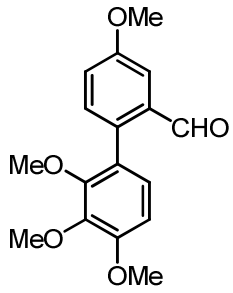
at the McMaster Regional Centre for Mass Spectrometry. Melting points were obtained using Thomas Hoover, Uni-Melt® capillary melting point apparatus.

Compounds containing a cobalt complex were kept away from hot conditions, prolonged exposure to air, and prolonged standing in solvent, and were stored at -20 ^{o}C in order to minimize decomposition. All of the reactions performed were accomplished under a atmosphere of nitrogen. Prior to reaction, the glassware was dried in an oven at 110 ^{o}C for 30 min and cooled in a dessicator.

2',3',4,4'-Tetramethoxybiphenyl-2-carbaldehyde (137)



General Procedure A. To a solution of 2-bromo-5-methoxybenzaldehyde (0.5700 g, 2.65 mmol) and tributyl(2,3,4-trimethoxyphenyl)stannane (1.4555 g, 3.18 mmol) in DMF (20 mL) was added CsF (0.8053 g, 5.3 mmol), $Pd(PPh_3)_4$ (0.3063 g, 0.26 mmol) and CuI (0.1009 g, 0.53 mmol). The reaction vessel was then placed under nitrogen atmosphere by vacuum purge three times. The resulting solution was heated to 45 ^{o}C for 12 h. Water was added and the mixture was extracted three times with CH_2Cl_2. The organic layer was dried with $MgSO_4$ to obtain the crude material as brown oil. Chromatographic purification (5:1 petroleum ether : Et_2O) afforded the intended product **(137)** (0.6665 g, 83%) as white crystals, mp. 102-3 ^{o}C (Lit. 102-3 ^{o}C).[1]

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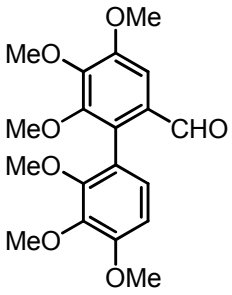
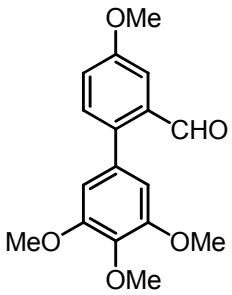
2',3',4,4',5,6-Hexamethoxybiphenyl-2-carbaldehyde (136)



Compound **(136)** was prepared according to General Procedure A, using 2-bromo-3,4,5-trimethoxybenzaldehyde (0.3043 g, 1.11 mmol) and tributyl(2,3,4-trimethoxyphenyl)stannane (0.6090 g, 1.33 mmol) as the starting materials. This produced (0.2998 g, 75 %) of **(136)** as a white powder after purification by radial chromatography (2:1 petroleum ether : Et_2O); IR (KBr) ν_{max} 2994, 2939, 2838, 1686; ^{1}H NMR δ 9.65 (s, 1H), 7.36 (s, 1H), 6.9 (d, J=8.5, 1H), 6.75 (d, J=8.5, 1H), 4.00 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H), 3.92 (s, 3H), 3.67 (s, 6H); ^{13}C NMR 191.4, 154.0, 153.1, 152.0, 151.6, 147.6, 142.1, 130.4, 129.8, 126.5, 119.4, 106.8, 104.9, 61.0, 61.0, 60.9, 60.7, 56.1, 56.0; HRMS m/e for $C_{19}H_{22}O_7$ calculated 362.1365 (M^+), found 362.1365.

3',4,4',5'-Tetramethoxybiphenyl-2-carbaldehyde (133)



General procedure A2.[2] The reagents, 2-bromo-5-methoxybenzaldehyde (0.7000 g, 3.26 mmol), 3,4,5-trimethoxyphenylboronic acid (0.3739 g, 4.7 mmol), $Pd(PPh_3)_4$ (0.5656 g, 0.65 mmol) and LiCl (0.4145 g, 9.8 mmol) were dissolved in DME (20 ml). To this mixture was added Na_2CO_3 (1.3820 g, 13.0 mmol) as a solution in degassed water (7 mL). The resulting solution was placed under a nitrogen atmosphere and heated to 80 ^{o}C for 12 h. Water was added and the reaction mixture was extracted three times with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to obtain the crude material as a brown oil. Radial chromatographic

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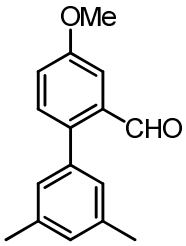
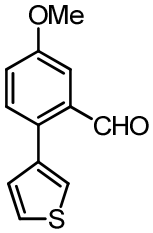
purification (4:1 petroleum ether : Et_2O) afforded the intended product **(133)** (0.7472 g, 76%) as white crystals, mp. 134-6 ^oC (Lit. 134-6 ^oC).[1]

4-Methoxy-3',5'-dimethylbiphenyl-2-carbaldehyde (134)



Compound (**134**) was prepared according to the General Procedure A2, using 2-bromo-5-methoxybenzaldehyde (0.2528 g, 1.2 mmol) and 3,5-dimethylphenylboronic acid (0.3525 g, 2.4 mmol) as the starting materials. This afforded the intended product **(134)** (0.2176 g, 77 %) as a white solid after purification using radial chromatography (15:1 petroleum ether : Et_2O), mp. 71-3 ^oC (Lit. 71-2 ^oC). [1]

5-Methoxy-2-(thiophen-3-yl)benzaldehyde (135)



Compound **(135)** was prepared according to the General Procedure A2, using 2-bromo-5-methoxybenzaldehyde (0.2255 g, 1.1 mmol) and 3-thienylboronic acid (0.2685 g, 2.1 mmol) as the starting materials. This afforded the intended product **(135)** (0.1808 g, 79 %) as a white solid after purification using radial chromatography (20:1 petroleum ether : Et_2O), mp. 68-70 ^oC (Lit. 68-9 ^oC).[1]

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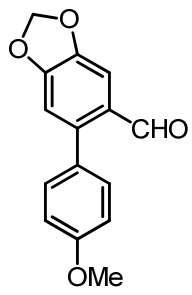
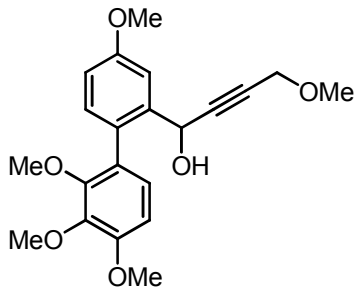
6-(4-Methoxyphenyl)benzo[d][1,3]dioxole-5-carbaldehyde (194)



Compound **(194)** was prepared according to the General Procedure A2, using 6-bromo-1,3-benzodioxole-5-carbaldehyde (0.7500 g, 3.3 mmol) and 4-methoxyphenylboronic acid (0.6967 g, 4.6 mmol) as the starting materials. This afforded the intended product **(194)** (0.6740 g, 80 %) as a white solid after purification using radial chromatography (3:1 petroleum ether : Et_2O), mp. 83-5 ^oC. IR (KBr) ν_{max} 3004, 2960, 2907, 2838, 1676; ^1H NMR δ 9.77 (s, 1H), 7.47 (s, 1H), 7.28 (d, J=8.7, 2H), 6.99 (d, J=8.7, 2H), 6.85 (s, 1H), 6.10 (s, 2H), 3.88 (s, 3H); ^{13}C NMR 190.9, 159.7, 152.1, 147.5, 143.5, 131.3, 129.8, 128.8, 113.8, 110.2, 106.2, 102.1, 55.4; HRMS m/e for $C_{15}H_{12}O_4$ calculated 256.0736 (M^+), found 256.0739.

4-Methoxy-1-(2',3',4,4'-tetramethoxybiphenyl-2-yl)but-2-yn-1-ol (141)



General Procedure B. A solution of MeLi (4.09 mL, 6.55 mmol) in Et_2O (1.60 M) was added dropwise to a solution of methyl propargyl ether (0.93 mL, 10.9 mmol) in THF (20 mL) at -78^oC. The resulting solution was stirred for 15 min. To this reaction mixture then was added a solution of aldehyde **(133)** (0.6603 g, 2.18 mmol) in THF (3 mL). The mixture at this point was warmed to room temperature, stirred for 1 h, and a solution of concentrated NH_4Cl was added subsequently. Extraction of the reaction mixture three times with Et_2O, followed by drying with $MgSO_4$, and concentration under reduced pressure afforded a crude product. Radial chromatographic purification (1:1 petroleum ether : Et_2O) yielded pure product **(141)** as a colorless oil (0.7014g, 86 %); IR (KBr) ν_{max} 3434(broad), 2995, 2937, 1485; ^1H NMR δ 7.46 (d, J=2.7,

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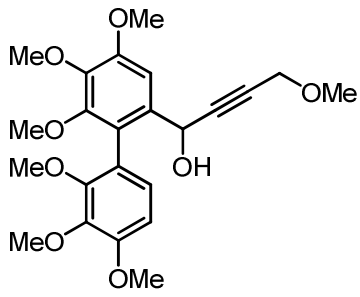
1H), 7.14 (d, J=8.4 1H), 6.93 (dd, J=8.4, 2.7, 1H), 6.90 (d, J=8.7, 1H), 6.78 (d, J=8.7, 1H), 5.30 (s, 1H), 4.16 (s, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H), 3.53 (s, 3H), 3.37 (s, 3H); ^{13}C NMR 159.7, 153.5, 150.8, 142.3, 141.1, 131.4, 128.7, 127.1, 125.9, 114.7, 112.7, 108.3, 86.4, 81.8, 63.0, 61.5, 61.4, 60.1, 57.7, 56.2, 55.5; HRMS m/e for $C_{21}H_{24}O_6$ calculated 372.1573 (M^+), found 372.1575.

1-(2',3',4,4',5,6-Hexamethoxybiphenyl-2-yl)-4-methoxybut-2-yn-1-ol (140)



Compound **(140)** was prepared by subjecting aldehyde **(136)** (0.0450 g, 0.12 mmol) to General Procedure B. This afforded desired product **(140)** (0.0527 g, 98 %) as a colorless solid after purification by radial chromatography (2 : 1 Et_2O : petroleum ether), mp. 117-9 ^oC. IR (KBr) ν_{max} 3445(broad), 2991, 2938, 2838, 1484; ^{1}H NMR δ 7.25 (s, 1H), 6.88 (d, J=8.5, 1H), 6.78 (d, J=8.5, 1H), 5.19 (s, 1H), 4.18 (s, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 3.92 (s, 3H), 3.91 (s, 3H), 3.72 (s, 3H), 3.64 (s, 3H), 3.60 (s, 1H), 3.39 (s, 3H); ^{13}C NMR 153.4, 151.4, 151.1, 142.3, 142.2, 135.7, 126.4, 123.3, 122.1, 107.8, 106.3, 86.2, 81.9, 62.7, 61.3, 61.2, 61.0, 60.8, 60.0, 57.6, 56.0, 55.9; HRMS m/e for $C_{23}H_{28}O_8$ calculated 432.1784 (M^+), found 432.1774.

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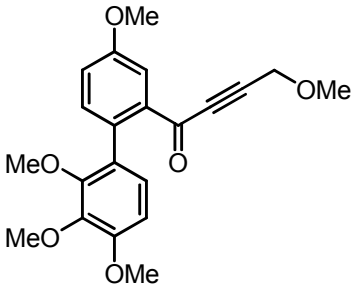
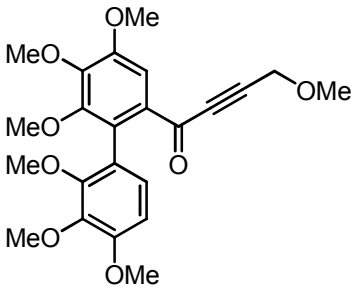
4-Methoxy-1-(2',3',4,4'-tetramethoxybiphenyl-2-yl)but-2-yn-1-one (143)



General Procedure C. To a solution of alcohol **(141)** (0.6420 g, 1.7 mmol) in CH_2Cl_2 (20 mL) at room temperature was added excess MnO_2 (0.7503 g). The reaction mixture was then stirred at room temperature and monitored by TLC. After complete consumption of the starting material (4 h) the reaction mixture was then filtered through a plug of silica and eluted with Et_2O. Purification by column chromatography (3:1 petroleum ether : Et_2O) gave product **(143)** (0.6131 g, 96 %) as a yellow oil. IR (KBr) ν_{max} 2996, 2938, 2836, 1652, 1483; ^{1}H NMR δ 7.47 (d, J=2.8, 1H), 7.28 (d, J=8.5, 1H), 7.13 (dd, J=8.5, 2.8, 1H), 6.93 (d, J=8.5, 1H), 6.72 (d, J=8.5, 1H), 4.05 (s, 2H), 3.90 (s, 6H), 3.89 (s, 3H), 3.58 (s, 3H), 3.25 (s, 3H); ^{13}C NMR 178.8, 158.6, 153.6, 151.2, 142.0, 138.1, 132.8, 130.7, 126.9, 124.9, 118.7, 114.1, 107.1, 89.2, 85.5, 61.0, 60.4, 59.5, 57.9, 56.1, 55.6; HRMS m/e for $C_{21}H_{22}O_6$ calculated 370.1416 (M^+), found 370.1410.

1-(2',3',4,4',5,6-Hexamethoxybiphenyl-2-yl)-4-methoxybut-2-yn-1-one (142)



Alcohol **(140)** (0.4463 g, 1.03 mmol) was subjected to General Procedure C. Upon purification by radial chromatography (2:1 petroleum ether : Et_2O) the anticipated product **(142)** was obtained (0.4078 g, 92 %) as a viscous yellow oil. IR (KBr) ν_{max} 2993, 2939, 2837, 1650, 1483; ^{1}H NMR δ 7.39 (s, 1H), 6.83 (d, J=8.5, 1H), 6.69 (d, J=8.5, 1H), 4.01 (s, 2H), 3.99 (s, 3H), 3.96 (s, 3H), 3.91 (s, 6H), 3.72 (s, 3H), 3.64 (s, 3H), 3.29 (s, 3H); ^{13}C NMR 177.6, 153.8, 152.4, 151.9, 151.7, 146.7,

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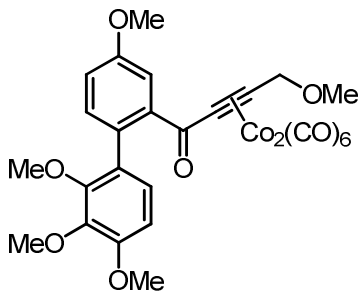
141.9, 132.4, 127.2, 126.1, 122.0, 108.9, 106.6, 90.2, 85.5, 61.0, 60.9, 60.8, 60.4, 59.5, 57.9, 56.1, 55.9; HRMS m/e for $C_{23}H_{26}O_8$ calculated 430.1628 (M^+), found 430.1626.

Hexacarbonyl[μ-η^4-(4-methoxy-1-(2',3',4,4'-tetramethoxybiphenyl-2-yl)but-2-yn-1-one)]dicobalt (145)



General Procedure D. To the solution of alkyne **(143)** (0.5751 g, 1.55 mmol) in CH_2Cl_2 (30 mL) at 0 ^oC was added excess of $Co_2(CO)_8$ (ca. 1.5 g). The solution was then warmed up to room temperature and monitored by TLC until consumption of the starting material was complete (1 h). The solvent was then removed under reduced pressure, and the residue was dissolved in petroleum ether. The solution was filtered through a plug of silica and eluted with petroleum ether in order to remove excess $Co_2(CO)_8$, subsequent elution with Et_2O afforded the crude product. Purification by column chromatography (5:1 petroleum ether : Et_2O) gave product **(145)** (0.9458 g, 93 %) as a dark red crystals mp. 82-4 ^oC. IR (KBr) ν_{max} 2997, 2938, 2836, 2099, 2067, 1649, 1483; ^1H NMR δ 7.33 (s, 1H), 7.29 (d, J=8.5, 1H), 7.03 (d, J=7.2, 1H), 6.93 (d, J=8.5, 1H), 6.72 (d, J=8.5, 1H), 4.59 (s, 2H), 3.88 (s, 9H), 3.58 (s, 3H), 3.53 (s, 3H); ^{13}C NMR 198.4, 195.5, 158.3, 153.2, 151.0, 142.4, 140.3, 132.9, 129.2, 127.5, 124.5, 116.4, 113.5, 107.2, 94.2, 87.1, 72.7, 60.9, 60.5, 59.1, 55.9, 55.5 ; HRMS m/e for $C_{27}H_{22}Co_2O_{12}$ calculated 571.9928 (M^+-3CO), found 571.9935.

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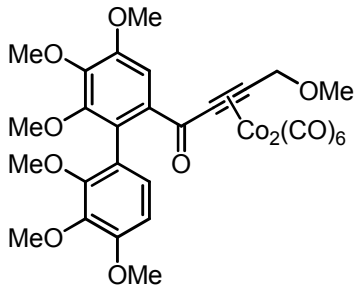
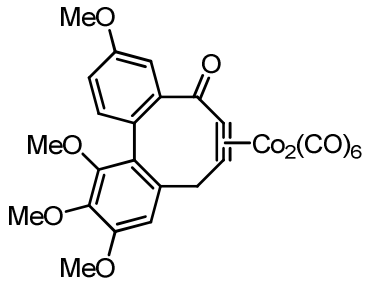
Hexacarbonyl[μ-η^4-(1-(2',3',4,4',5,6-hexamethoxybiphenyl-2-yl)-4-methoxybut-2-yn-1-one)]dicobalt (144)



Alkyne **(142)** (0.1743 g, 0.40 mmol) was subjected to General Procedure D. Following purification by column chromatography (3:1 petroleum ether : Et_2O) the product **(144)** was acquired (0.2696 g, 93 %) as a dark red oil. IR (KBr) ν_{max} 2993, 2940, 2827, 2099, 2068, 1650, 1484; ^{1}H NMR δ 7.22 (s, 1H), 6.83 (d, J=8.5, 1H), 6.66 (d, J=8.5, 1H), 4.71 (1/2 $AB_{quartet}$, J=13.0, 1H), 4.70 (1/2 $AB_{quartet}$, J = 13.0, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.69 (s, 3H), 3.66 (s, 3H), 3.54 (s, 3H); ^{13}C NMR 198.3, 194.5, 153.1, 152.3, 151.9, 151.5, 144.7, 142.0, 135.2, 125.0, 124.9, 122.7, 107.2, 106.5, 93.7, 87.8, 73.0, 61.0, 60.9, 60.8, 60.3, 59.2, 56.1, 55.8; HRMS m/e for $C_{29}H_{26}Co_2O_{14}$ calculated 632.0139 (M^+-3CO), found 632.0155.

Hexacarbonyl[μ-η^4-(1,2,3,9-tetramethoxy-5H-dibenzo[a,c]cyclooctyn-3-one)]dicobalt (147)



General Procedure E. Acyclic alkyne complex **(145)** (0.4135 g, 0.63 mmol) was dissolved in CH_2Cl_2 (160 mL) (4.0 x 10^{-3} mol/L). The reaction mixture was cooled to 0 ^{o}C, and BF_3-OEt_2 (0.24 ml, 1.89 mmol) was added via syringe. The reaction was warmed to room temperature and the progress of the reaction was monitored by TLC. Upon completion (4 h) the reaction mixture was quenched with a concentrated solution of NH_4Cl and extracted three times with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, which gave

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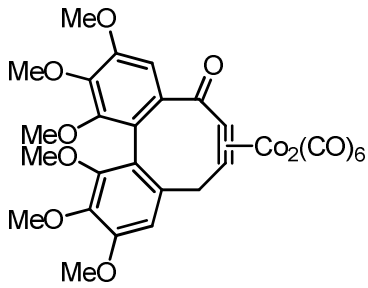
the crude product as a dark red oil. Purification by column chromatography (7:1 petroleum ether : Et_2O) afforded the intended product **(147)** (0.3353 g, 85 %) as a dark red solid, mp. 141-2 ^oC. IR (KBr) ν_{max} 3000, 2940, 2837, 2099, 2066, 1658, 1483; ^1H NMR δ 7.11 (d, J=8.5, 1H), 7.01 (dd, J=8.5, 2.7, 1H), 6.98 (d, J=2.7, 1H), 6.57 (s, 1H), 3.89 (d, J=15.0, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.80 (d, J=15.0, 1H), 3.46 (s, 3H); ^{13}C NMR 198.4, 197.9, 159.1, 154.0, 152.6, 144.1, 141.8, 137.2, 133.0, 125.3, 125.1, 115.8, 110.6, 107.5, 102.7, 85.1, 61.1, 61.0, 56.1, 55.5, 40.0; HRMS m/e for $C_{26}H_{18}Co_2O_{11}$ calculated 595.9564 (M^+-CO), found 595.9576.

Hexacarbonyl[μ-η^4-(1,2,3,9,10,11-hexamethoxy-5H-dibenzo[a,c]cyclooctyn-3-one)]dicobalt (146)



Acyclic alkyne complex **(144)** (0.6300 g, 0.88 mmol) was subjected to the reaction conditions described in General Procedure E. Following purification by column chromatography (3:1 petroleum ether : Et_2O) product **(146)** was obtained (0.4901 g, 81 %) as a dark red crystals, mp. 108-9 ^oC. IR (KBr) ν_{max} 2996, 2941, 2837, 2098, 2062, 1659, 1483; ^1H NMR δ 6.79 (s, 1H), 6.58 (s, 1H), 3.91 (s, 3H), 3.90 (d, J=15.0, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.81 (d, J=15.0, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.52 (s,3H); ^{13}C NMR 197.9, 197.7, 154.0, 153.4, 152.8, 151.9, 143.5, 141.7, 138.8, 137.3, 120.9, 120.1, 107.5, 105.0, 102.8, 85.5, 61.0, 60.9, 60.8, 56.1, 56.0, 40.2; HRMS m/e for $C_{28}H_{22}Co_2O_{13}$ calculated 571.9928 (M^+-4CO), found 571.9936.

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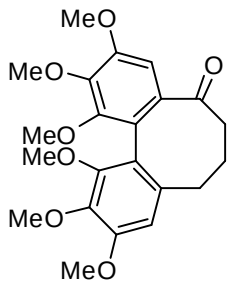
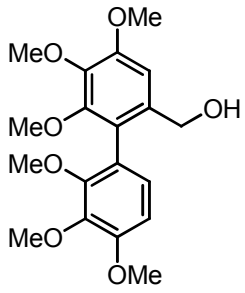
1,2,3,9,10,11-hexamethoxy-5H-dibenzo[a,c]cyclooctan-3-one (158)



To the stirred solution of complex **(146)** (0.0517 g, 0.075 mmol) in degassed benzene (5 mL) was added Bu_3SnH (0.219 mL, 0.756 mmol). The mixture was heated to 65 ^oC and reaction progress was monitored by TLC. Upon consumption of starting material (3 h) the reaction mixture was cooled to room temperature and concentrated under reduced pressure. Filtration of crude material through a plug of silica, followed by purification by radial chromatography (1 : 1 petroleum ether : Et_2O) gave ketone product **(158)** (0.0249 g, 82 %) as viscous colorless oil. ^1H NMR δ 7.50 (s, 1H), 6.53 (s, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.92 (s, 3H), 3.90 (s, 3H), 3.63 (s, 3H), 3.54 (s, 3H), 2.64 (m, 1H), 2.50 (m, 2H), 2.32 (m, 1H), 1.97 (m, 1H), 1.72 (m, 1H).

(2',3',4,4',5,6-Hexamethoxybiphenyl-2-yl)methanol (161)



General Procedure F. Aldehyde **(136)** (0.1213 g, 0.33 mmol) was dissolved in anhydrous ethanol (5 mL). To this solution was added $NaBH_4$ (0.0254 g, 0.67 mmol) at room temperature. The reaction was monitored by TLC until complete consumption of the starting material (0.5 h); the reaction was then slowly quenched with a saturated solution of $NH_4Cl_{(aq)}$. The mixture was then diluted with diethyl ether and extracted three times. The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to afford an oily residue. Further purification by radial chromatography (2:1 Et_2O : petroleum ether) produced the intended product **(161)** (0.1138 g, 93 %) as a viscous colorless oil. IR (KBr) ν_{max} 3487(broad), 2938, 2838, 1596, 1485; ^1H NMR δ 6.87 (s, 1H), 6.83 (d, J=8.5, 1H), 6.74

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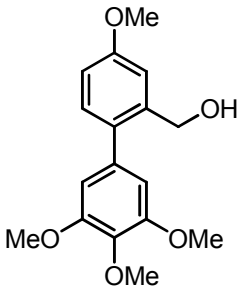
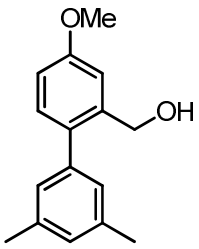
(d, J=8.5, 1H), 4.25 (s, 2H), 3.92 (s, 3H), 3.90 (s, 6H), 3.89 (s, 3H), 3.70 (s, 3H), 3.64 (s, 3H), 2.75 (s, 1H); ^{13}C NMR 153.1, 153.0, 151.6, 151.3, 142.2, 141.6. 135.5, 126.0, 123.7, 122.7, 107.8, 107.4, 63.9, 61.1, 61.0, 60.9, 60.8, 56.0, 55.9; HRMS m/e for $C_{19}H_{24}O_7$ calculated 364.1522 (M^+), found 364.1529.

(3',4,4',5'-Tetramethoxybiphenyl-2-yl)methanol (159)



Aldehyde **(137)** (0.2040 g, 0.67 mmol) was subjected to General Procedure F. Upon purification by radial chromatography (1:1 petroleum ether : Et_2O) the anticipated product **(159)** was obtained (0.2049 g, 99 %) as a viscous colorless oil. IR (KBr) ν_{max} 3473(broad), 2998, 2937, 2836, 1585, 1491; ^{1}H NMR δ 7.22 (d, J=8.4, 1H), 7.10 (d, J=2.7, 1H), 6.87 (dd, J=8.4, 2.7, 1H), 6.56 (s, 2H), 4.60 (s, 2H), 3.88 (s, 3H), 3.84 (s, 9H), 2.05 (s, 1H); ^{13}C NMR 159.2, 152.9, 139.4, 137.0, 136.1, 133.7, 130.9, 113.5, 113.1, 106.5, 63.2, 60.9, 56.1, 55.4; HRMS m/e for $C_{17}H_{20}O_5$ calculated 304.1311 (M^+), found 304.1310.

(4-Methoxy-3',5'-dimethylbiphenyl-2-yl)methanol (160)



Aldehyde **(134)** (0.0517 g, 0.21 mmol) was subjected to General Procedure F. Upon purification by radial chromatography (1:1 petroleum ether : Et_2O) the anticipated product **(160)** was obtained (0.0479 g, 92 %) as a thick colorless oil. IR (KBr) ν_{max} 3384(broad), 3000, 2918, 2859, 1606, 1500; ^{1}H NMR δ 7.19 (d, J=8.4, 1H), 7.11 (d, J=2.7, 1H), 6.99 (s, 1H), 6.94 (s, 2H), 6.88 (dd, J=8.4, 2.7, 1H), 4.61 (s, 1H), 3.87 (s, 3H), 2.36 (s, 6H), 1.61 (s, 1H); ^{13}C NMR 159.1, 140.3, 139.4,

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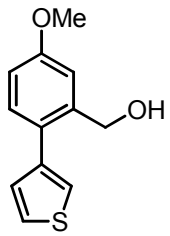
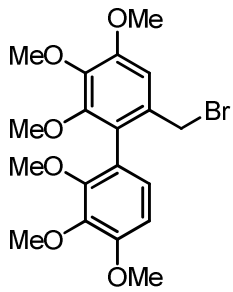
137.8, 133.8, 131.1, 128.6, 127.1, 113.2, 113.1, 63.3, 55.4, 21.4; HRMS m/e for $C_{16}H_{18}O_2$ calculated 242.1307 (M^+), found 242.1308.

(5-Methoxy-2-(thiophen-3-yl)phenyl)methanol (162)



Aldehyde **(135)** (0.1322 g, 0.61 mmol) was subjected to General Procedure F. Upon purification by radial chromatography (2:1 petroleum ether : ether) the anticipated product **(162)** was obtained (0.1181 g, 89 %) as a colorless solid, mp. 101-3 ^oC. IR (KBr) ν_{max} 3312(broad), 2952, 2914, 2837, 1609, 1487; ^1H NMR 7.39 (dd, J=4.9, 3.0, 1H), 7.31 (d, J=8.5, 1H), 7.29 (dd, J=3.0, 1.3, 1H), 7.18 (dd, J=4.9, 1.3, 1H), 7.10 (d, J=2.7, 1H), 6.89 (dd, J=8.5, 2.7, 1H), 4.66 (s, 2H), 3.86 (s, 3H), 1.65 (s, 1H); ^{13}C NMR 159.2, 140.5, 139.5, 131.1, 128.9, 128.4, 125.3, 122.5, 113.8, 113.3, 63.5, 55.3; MS m/e 218(M^+), HRMS m/e for $C_{12}H_{12}O_2S$ calculated 220.0558 (M^+), found 220.0563.

6-(Bromomethyl)-2,2',3,3',4,4'-hexamethoxybiphenyl (165)



General Procedure G. To a stirred solution of benzyl alcohol **(161)** (0.1138 g, 0.31 mmol) in Et_2O (10 mL) at room temperature, was added PBr_3 (0.038 mL, 0.40 mmol). The reaction mixture was heated to reflux for 2 h, after which TLC showed complete consumption of the starting material. After cooling to room temperature, the reaction mixture was slowly diluted with a saturated $NaHCO_{3(aq)}$ solution and extracted three times with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to obtain an oily residue. Purification by radial chromatography (4:1 petroleum ether : Et_2O) afforded the

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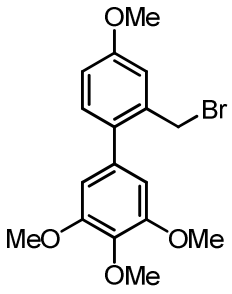
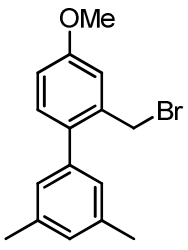
intended product **(165)** (0.1308 g, 99 %) as a thick colorless oil. IR (KBr) ν_{max} 2937, 2837, 1595, 1486; ^{1}H NMR δ 6.92 (d, J=8.4, 1H), 6.83 (s, 1H), 6.74 (d, J=8.4, 1H), 4.37 (d, J=10.0, 1H), 4.19 (d, J=10.0, 1H), 3.91 (s, 6H), 3.90 (s, 6H), 3.70 (s, 3H), 3.67 (s, 3H); ^{13}C NMR 153.5, 153.0, 151.8, 142.3, 142.1, 131.7, 125.6, 121.9, 108.8, 106.8, 61.0, 60.9, 60.8, 56.0, 55.9, 32.8.; HRMS m/e for $C_{19}H_{23}BrO_6$ calculated 426.0678 (M^+), found 426.0685.

2-(Bromomethyl)-3',4,4',5'-tetramethoxybiphenyl (163)



Alcohol **(159)** (0.0730 g, 0.24 mmol) was subjected to the conditions described in General Procedure G. This afforded the desired product **(163)** (0.0703 g, 80 %) as a colorless solid after purification by radial chromatography (4 : 1 petroleum ether : Et_2O), mp. 119-120 ^{o}C. IR (KBr) ν_{max} 3011, 2952, 2836, 1587, 1494; ^{1}H NMR δ 7.22 (d, J=8.5, 1H), 7.05 (d, J=2.7, 1H), 6.91 (dd, J=8.5, 2.7, 1H), 6.68 (s, 2H), 4.46 (s, 2H), 3.91 (s, 3H), 3.90 (s, 6H), 3.86 (s, 3H); ^{13}C NMR 159.1, 152.9, 136.2, 135.5, 134.6, 131.3, 115.7, 114.8, 106.4, 60.9, 56.2, 55.5, 32.8; HRMS m/e for $C_{17}H_{19}BrO_4$ calculated 366.0467 (M^+), found 366.0471.

2-(Bromomethyl)-4-methoxy-3',5'-dimethylbiphenyl (164)

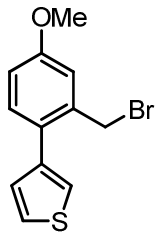


Alcohol **(160)** (0.0479 g, 0.20 mmol) was subjected to the conditions described in General Procedure G. This afforded the desired product **(164)** (0.0382 g, 63 %) as a colorless solid after purification by radial chromatography (25 : 1 petroleum ether : Et_2O), mp. 66-8 ^{o}C. IR (KBr) ν_{max} 3384 $_{(broad)}$, 3004, 2916, 2837, 1606, 1501; ^{1}H NMR δ 7.18 (d, J=8.4, 1H), 7.06 (d, J=2.7,

References start on page 109.

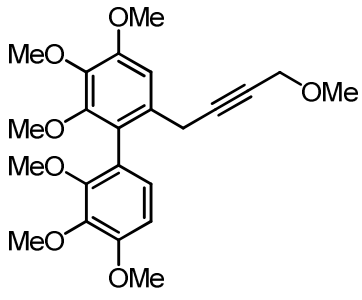
1H), 7.05 (s, 2H), 7.02 (s, 1H), 6.90 (dd, J=8.4, 2.7, 1H), 4.46 (s, 2H), 3.87 (s, 3H), 2.38 (s, 6H); ^{13}C NMR 158.9, 139.8, 137.7, 136.2, 134.9, 131.4, 128.8, 127.0, 115.5, 114.6, 55.4, 32.5, 21.3; HRMS m/e for $C_{16}H_{17}BrO$ calculated 304.0463 (M^+), found 304.0468.

3-(2-(Bromomethyl)-4-methoxyphenyl)thiophene (166)



Alcohol **(162)** (0.1084 g, 0.49 mmol) was subjected to the conditions described in General Procedure G. This afforded the desired product **(166)** (0.1016 g, 73 %) as a colorless solid after purification by radial chromatography (20 : 1 petroleum ether : Et_2O), mp. 84-5 ^{o}C. IR (KBr) ν_{max} 3006, 2961, 2836, 1614, 1493; ^{1}H NMR 7.42 (dd, J=4.9, 3.0, 1H), 7.41 (dd, J=3.0, 1.3, 1H), 7.28 (d, J=8.5, 1H), 7.26 (dd, J=4.9, 1.3, 1H), 7.05 (d, J=2.7, 1H), 6.91 (dd, J=8.5, 2.7, 1H), 4.51 (s, 2H), 3.87 (s, 3H); ^{13}C NMR 159.1, 140.1, 136.5, 131.5, 129.2, 128.9, 125.5, 122.7, 115.8, 114.8, 55.4, 32.7; HRMS m/e for $C_{12}H_{11}BrOS$ calculated 281.9714 (M^+), found 281.9713.

2,2',3,3',4,4'-Hexamethoxy-6-(4-methoxybut-2-ynyl)biphenyl (169)



General Procedure H. *n*-BuLi (1.20 mL, 1.97 mmol, 1.60 M solution in hexanes) was added to a solution of methyl propargyl ether (0.221 mL, 2.62 mmol) in THF (5 mL) at -78 ^{o}C. The reaction mixture was stirred for 30 min at -78 ^{o}C, and then to it was added $InCl_3$ (0.1449 g, 0.65 mmol) as a solution in THF (1 mL). The cooling bath was removed and reaction mixture was allowed to warm to room temperature; at this point $Pd(dppf)Cl_2$ (0.0100 g, 2 mol %) and benzyl bromide **(165)** (0.2797 g, 0.65 mmol) as a suspension in THF (1 mL) were added. The resulting solution

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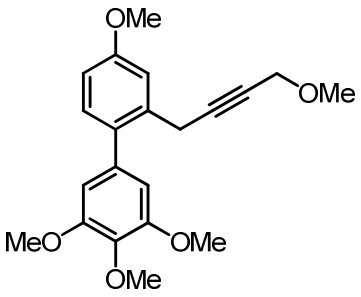
was heated to reflux for 12 h. The reaction mixture was allowed to cool to room temperature, diluted with a saturated solution of $NaHCO_3$, and extracted three times with Et_2O. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to obtain an oily residue. Purification by radial chromatography (2:1 petroleum ether : Et_2O) afforded the intended product **(169)** (0.1894 g, 69 %) as a viscous yellow oil. IR (KBr) ν_{max} 2937, 2837, 1596, 1484; ^{1}H NMR δ 6.99 (s, 1H), 6.81 (d, J=8.4, 1H), 6.72 (d, J=8.4, 1H), 4.12 (s, 2H), 3.94 (s, 3H), 3.92 (s, 8H), 3.89 (s, 3H), 3.69 (s, 3H), 3.67 (s, 3H), 3.38 (s, 3H); ^{13}C NMR 153.2, 152.8, 151.8, 151.7, 142.3, 140.7, 131.0, 125.7, 124.2, 122.8, 107.3, 107.0, 85.0, 78.0, 60.9, 60.8, 60.7, 60.2, 57.4, 56.0, 23.2.; HRMS m/e for $C_{23}H_{28}O_7$ calculated 416.1835 (M^+), found 416.1841.

3',4,4',5'-Tetramethoxy-2-(4-methoxybut-2-ynyl)biphenyl (167)

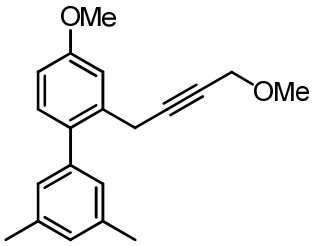


MeLi (0.72 mL, 1.15 mmol, 1.60 M solution in hexanes) was added to methyl propargyl ether (0.129 mL, 1.53 mmol) in Et_2O (10 mL) at -78^{o}C. After 0.5 h, benzyl bromide **(163)** (0.0703 g, 0.19 mmol) was added as a solution in Et_2O (1 mL). The cooling bath was removed and reaction was warmed to room temperature and stirred for 12 h. The solution was quenched with water and extracted three times with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure which gave the crude product. Purification by radial chromatography (3:1 petroleum ether : Et_2O) granted the intended product **(167)** (0.0416 g, 61 %) as a viscous colorless oil. IR (KBr) ν_{max} 3061, 2995, 2835, 1584, 1491; ^{1}H NMR δ 7.21 (d, J=8.5, 1H), 7.13 (d, J=2.7, 1H), 6.85 (dd, J=8.5, 2.7, 1H), 6.55 (s, 2H), 4.12 (s, 2H),

References start on page 109.

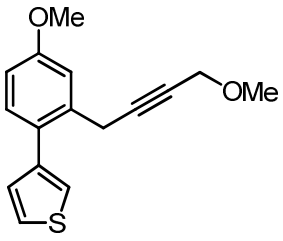
3.90 (s, 3H), 3.87 (s, 6H), 3.86 (s, 3H), 3.54 (s, 2H), 3.37 (s, 3H); ^{13}C NMR 159.1, 152.9, 136.9, 136.2, 135.5, 134.0, 130.8, 114.6, 112.2, 106.5, 85.2, 78.0, 60.9, 60.2, 57.5, 56.1, 55.3, 23.7; HRMS m/e for $C_{21}H_{24}O_5$calculated 356.1624 (M^+), found 356.1617.

4-Methoxy-2-(4-methoxybut-2-ynyl)-3',5'-dimethylbiphenyl (168)



Aryl bromide **(164)** (0.0460 g, 0.15 mmol) was subjected to General Procedure H. This afforded the desired product **(168)** (0.0293 g, 66 %) as a clear thick oil after purification by radial chromatography (15 : 1 petroleum ether : Et_2O). IR (KBr) ν_{max} 2996, 2923, 2836, 1608, 1501, 1464; ^{1}H NMR δ 7.18 (d, J=2.6, 1H), 7.15 (d, J=8.4, 1H), 6.98 (s, 1H), 6.93 (s, 2H), 6.84 (dd, J=8.4, 2.6, 1H), 4.14 (s, 2H), 3.87 (s, 3H), 3.54 (s, 2H), 3.40 (s, 3H), 2.35 (s, 6H); ^{13}C NMR 159.0, 140.6, 137.7, 135.4, 134.2, 130.9, 128.5, 127.2, 114.4, 112.0, 85.2, 78.0, 60.2, 57.4, 55.3, 23.6, 21.3; HRMS m/e for $C_{20}H_{22}O_2$ calculated 294.1620 (M^+), found .

3-(4-Methoxy-2-(4-methoxybut-2-ynyl)phenyl)thiophene (170)

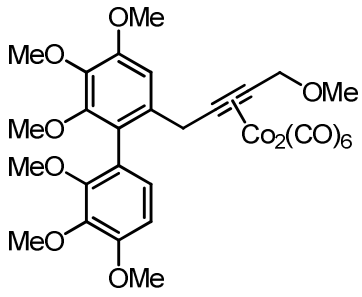


Aryl bromide **(166)** (0.1399 g, 0.49 mmol) was subjected to General Procedure H. This afforded the desired product **(170)** (0.0822 g, 61 %) as a viscous, colorless oil after purification by radial chromatography (15 : 1 petroleum ether : Et_2O). IR (KBr) ν_{max} 2994, 2935, 2835, 1608, 1491; ^{1}H NMR 7.37 (dd, J=4.9, 3.0, 1H), 7.25 (d, J=8.5, 1H), 7.23 (dd, J=3.0, 1.3, 1H), 7.15 (d, J=2.7, 1H), 7.13 (dd, J=4.9, 1.3, 1H), 6.83 (dd, J=8.5, 2.7, 1H), 4.13 (s, 2H), 3.86 (s, 3H), 3.59 (s, 2H), 3.38 (s, 3H); ^{13}C NMR 159.1, 140.8, 135.8, 131.0,

References start on page 109.

128.9, 128.5, 125.2, 122.5, 114.6, 112.2, 85.0, 78.1, 60.2, 57.5, 55.3, 23.8; HRMS m/e for $C_{16}H_{16}O_2S$ calculated 272.0871 (M^+), found 272.0875.

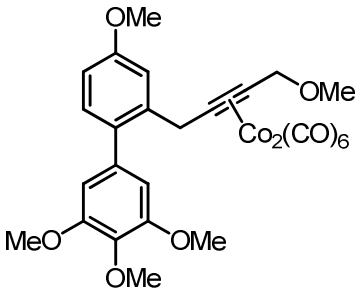
Hexacarbonyl[μ-η^4-(2,2',3,3',4,4'-hexamethoxy-6-(4-methoxybut-2-ynyl)biphenyl)]dicobalt (173)



Alkyne **(169)** (0.1318 g, 0.32 mmol) was subjected to conditions described in General Procedure D. This afforded the desired alkyne complex product **(173)** (0.2211 g, 99 %) as a viscous red oil after purification by column chromatography (3 : 1 petroleum ether : Et_2O). IR (KBr) ν_{max} 2992, 2938, 2825, 2089, 2053, 1596, 1486; ^{1}H NMR δ 6.88 (d, J=8.4, 1H), 6.81 (s, 1H), 6.73 (d, J=8.4, 1H), 4.54 (1/2 $AB_{quartet}$, J=13.0, 1H), 4.47 (1/2 $AB_{quartet}$, J=13.0, 1H) 3.97 (1/2 $AB_{quartet}$, J=13.0, 1H), 3.93 (s, 3H), 3.91 (1/2 $AB_{quartet}$, J=13.0, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.65 (s, 3H), 3.63 (s, 3H), 3.47 (s, 3H); ^{13}C NMR 199.6, 153.2, 152.6, 151.6, 151.4, 142.2, 141.2, 134.7, 126.4, 124.3, 122.6, 108.5, 107.0, 97.6, 93.3, 73.2, 60.9, 60.7, 60.6, 58.9, 56.0, 55.0, 55.7, 37.2; HRMS m/e for $C_{29}H_{28}Co_2O_{13}$ calculated 618.0346 (M^+ -3CO), found 618.0339.

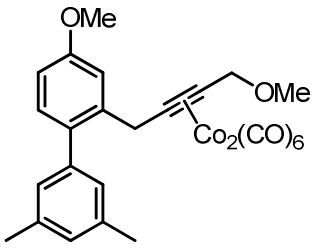
References start on page 109.

Hexacarbonyl[μ-η^4-(3',4,4',5'-tetramethoxy-2-(4-methoxybut-2-ynyl)biphenyl)]dicobalt (171)



Alkyne **(167)** (0.0416 g, 0.1168 mmol) was subjected to the conditions described in General Procedure D. This afforded the desired alkyne complex product **(171)** (0.0646 g, 78 %) as a viscous dark red oil after purification by column chromatography (4 : 1 petroleum ether : Et_2O). IR (KBr) ν_{max} 2997, 2937, 2833, 2089, 2050, 2021, 1583, 1492; ^{1}H NMR δ 7.21 (d, J=8.5, 1H), 6.96 (d, J=2.7, 1H), 6.85 (dd, J=8.5, 2.7, 1H), 6.56 (s, 2H), 4.39 (s, 2H), 4.28 (s, 2H), 3.89 (s, 6H), 3.86 (s, 3H), 3.85 (s, 3H), 3.46 (s, 3H); ^{13}C NMR 199.4, 158.9, 153.0, 138.3, 137.2, 136.3, 134.0, 131.5, 115.7, 112.8, 107.2, 97.3, 93.5, 72.9, 60.8, 58.9, 56.2, 55.2, 36.6; HRMS m/e for $C_{27}H_{24}Co_2O_{11}$ calculated 641.9983 (M^+), found.

Hexacarbonyl[μ-η^4(4-methoxy-2-(4-methoxybut-2-ynyl)-3',5'-dimethylbiphenyl)]dicobalt (172)



Alkyne **(168)** (0.0174 g, 0.0592 mmol) was subjected to the conditions described in General Procedure D. This afforded the desired alkyne complex product **(172)** (0.0295 g, 86 %) as a viscous dark red oil after purification by column chromatography (20 : 1 petroleum ether : Et_2O). IR (KBr) ν_{max} 2999, 2922, 2819, 2090, 2048, 1606, 1465; ^{1}H NMR δ 7.17 (d, J=8.4, 1H), 6.96 (s, 3H), 6.95 (d, J=2.7, 1H), 6.84 (dd, J=8.4, 2.7, 1H), 4.33 (s, 2H), 4.23 (s, 2H), 3.85 (s, 3H), 3.45 (s, 3H), 2.35 (s, 6H); ^{13}C NMR 199.4, 158.8, 140.6,

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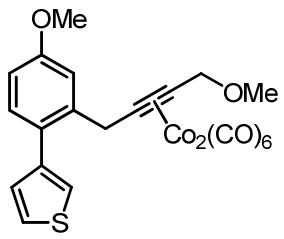
138.4, 137.8, 134.3, 131.5, 128.4, 127.5, 115.5, 112.7, 97.3, 93.5, 72.9, 58.9, 55.2, 36.9, 21.3; HRMS m/e for $C_{26}H_{22}Co_2O_8$ calculated 579.9979 (M^+), found .

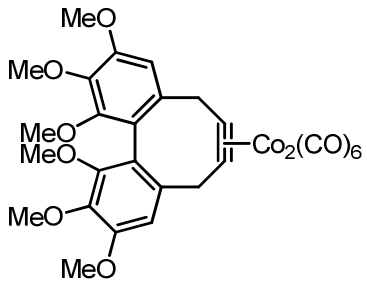
Hexacarbonyl[μ-η^4(3-(4-methoxy-2-(4-methoxybut-2-ynyl)phenyl)thiophene)]dicobalt (174)



Alkyne **(170)** (0.0174 g, 0.0640 mmol) was subjected to the conditions described in General Procedure D. This afforded the desired alkyne complex product **(174)** (0.0295 g, 86 %) as a viscous dark red oil after purification by column chromatography (20 : 1 petroleum ether : Et_2O). IR (KBr) ν_{max} 2996, 2932, 2821, 2089, 2050, 2020, 1608, 1493; ^{1}H NMR 7.43 (dd, J=4.9, 3.0, 1H), 7.30 (d, J=3.0, 1H), 7.26 (s, 1H), 7.21 (d, J=4.9, 1H), 6.99 (d, J=2.6, 1H), 6.89 (dd, J=8.5, 2.6, 1H), 4.39 (s, 2H), 4.33 (s, 2H), 3.90 (s, 3H), 3.50 (s, 3H); ^{13}C NMR 199.4, 159.1, 141.2, 138.8, 131.8, 129.1, 128.7, 125.7, 122.7, 115.9, 113.0, 97.3, 93.6, 72.8, 59.0, 55.3, 37.1; HRMS m/e for $C_{22}H_{16}Co_2O_8S$ calculated 473.9382 (M^+-3CO), found 473.9373.

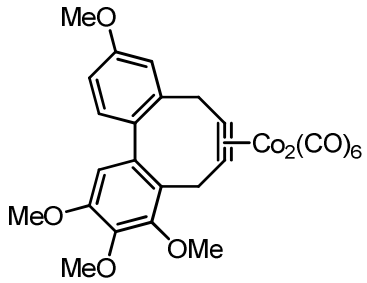
References start on page 109.

Hexacarbonyl[μ-η^4-(1,2,3,9,10,11-hexamethoxy-5H-dibenzo[a,c]cyclooctyne)]dicobalt (177)



Compound **(177)** was prepared according to General Procedure E, by using acyclic alkyne complex **(173)** (0.2075 g, 0.30 mmol) in shorter reaction time (1 h). This afforded the intended cyclic alkyne complex (0.1875 g, 93 %) as dark red crystals after purification using column chromatography (3:1 petroleum ether : Et_2O), mp. 133-4 ^oC. IR (KBr) ν_{max} 2995, 2940, 2834, 2089, 2049, 1594, 1484; ^1H NMR δ 6.58 (s, 2H), 3.89 (s, 6H), 3.84 (s, 6H), 3.77 (1/2 $AB_{quartet}$, J=15.0, 2H), 3.70 (s, 6H), 3.68 (1/2 $AB_{quartet}$, J=15.0, 2H); ^{13}C NMR 199.6, 152.8, 152.1, 141.3, 135.1, 123.0, 107.8, 101.1, 60.9, 60.5, 56.0, 40.1; HRMS m/e for $C_{28}H_{24}Co_2O_{12}$ calculated 669.9932 (M^+), found 669.9926.

Hexacarbonyl[μ-η^4-(2,3,4,9-tetramethoxy-5H-dibenzo[a,c]cyclooctyne)]dicobalt (174)



Compound **(174)** was prepared according to General Procedure E, by using acyclic alkyne complex **(171)** (0.0498 g, 0.0776 mmol) in shorter reaction time (1 h). This afforded the intended cyclic alkyne complex **(174)** (0.0429 g, 91 %) as a dark red solid after purification using column chromatography (4:1 petroleum ether : Et_2O), mp. 118-120 ^oC. IR (KBr) ν_{max} 2999, 2940, 2836, 2087, 2047, 2016, 1606, 1483; ^1H NMR δ 7.13 (d, J=8.3, 1H), 6.84 (dd, J=8.3, 2.7, 1H), 6.77 (d, J=2.7, 1H), 6.51 (s, 1H), 4.33 (d, J=15.0, 1H), 3.97 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.80 (1/2 $AB_{quartet}$, J=15.0, 1H), 3.72 (1/2 $AB_{quartet}$, J=15.0, 1H), 3.26 (d,

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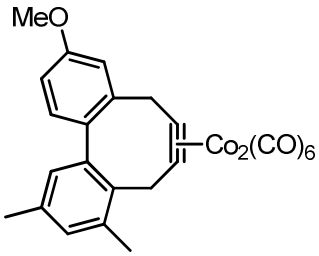
J=15.0, 1H); ^{13}C NMR 199.8, 159.2, 151.8, 150.3, 141.2, 140.1, 137.2, 133.9, 131.1, 125.8, 114.2, 111.8, 109.7, 101.9, 100.8, 61.2, 60.5, 56.0, 55.5, 40.1, 31.1; HRMS m/e for $C_{26}H_{20}Co_2O_{10}$ calculated 609.9720 (M^+), found 609.9694.

Hexacarbonyl[μ-η^4-(9-methoxy-2,4-dimethyl-5H-dibenzo[a,c]cyclooctyne)]dicobalt (176)



Compound **(176)** was prepared according to General Procedure E, by using acyclic alkyne complex **(172)** (0.0295 g, 0.0509 mmol). This afforded the intended cyclic alkyne complex **(176)** (0.0246 g, 88 %) as a dark red solid after purification using column chromatography (20:1 petroleum ether : Et_2O), mp. 106-8 ^oC. IR (KBr) ν_{max} 3001, 2959, 2836, 2087, 2048, 2016, 1606, 1499; ^{1}H NMR δ 7.10 (d, J=8.3, 1H), 6.97 (s, 1H), 6.84 (dd, J=8.3, 2.7, 1H), 6.83 (s, 1H), 6.77 (d, J=2.7, 1H), 4.15 (d, J=15.0, 1H), 3.83 (s, 3H), 3.79 (1/2 $AB_{quartet}$, J=15.0, 1H), 3.73 (1/2 $AB_{quartet}$, J=15.0, 1H), 3.47 (d, J=15.0, 1H), 2.42 (s, 3H), 2.29 (s, 3H); ^{13}C NMR 199.7, 159.1, 142.0, 139.7, 136.0, 134.8, 134.3, 130.9, 130.4, 129.2, 114.1, 111.7, 101.8, 100.7, 55.4, 40.3, 34.4, 20.9, 19.9; HRMS m/e for $C_{25}H_{18}Co_2O_7$ calculated 547.9716 (M^+), found.

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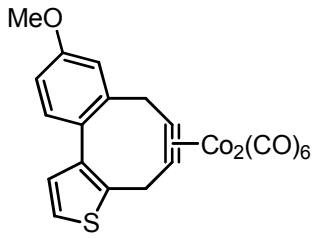
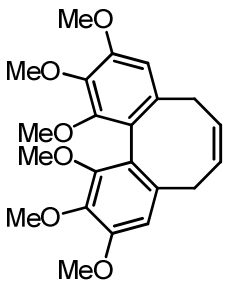
Hexacarbonyl[μ-η^4-(8-methoxy-4H-benzo[3,4]cyclooctyne-[1,2-b]thiophene]dicobalt (178)



Compound **(178)** was prepared according to General Procedure E, by using acyclic alkyne complex **(174)** (0.0186 g, 0.0333 mmol). This afforded the intended cyclic alkyne complex **(178)** (0.0136 g, 77 %) as a dark red oil after purification using column chromatography (25:1 petroleum ether : Et_2O). IR (KBr) ν_{max} 3003, 2934, 2852, 2089, 2050, 2017, 1608, 1494; ^{1}H NMR 7.15 (d, J=8.1, 1H), 7.14 (d, J=5.1, 1H), 6.93 (d, J=5.1, 1H), 6.84 (dd, J=10.6, 2.7, 1H), 4.09 (d, J=15.0, 1H), 3.93 (d, J=15.0, 1H), 3.84 (s, 3H), 3.83 (d, J=15.0, 1H), 3.78 (d, J=15.0, 2H); ^{13}C NMR 199.4, 159.1, 141.2, 138.8, 131.8, 129.1, 128.7, 125.7, 122.7, 115.9, 113.0, 97.3, 93.6, 72.8, 59.0, 55.3, 37.1; HRMS m/e for $C_{22}H_{16}Co_2O_8S$ calculated 525.8968 (M^+-CO), found 525.8976.

1,2,3,9,10,11-Hexamethoxy-5H-dibenzo[a,c]cyclooctene (180)



General Procedure I. Triethylsilane (0.521 mL, 3.26 mmol) was added to a mixture of the cyclooctyne complex **(177)** (0.4457 g, 0.65 mmol) and bis(trimethylsilyl)acetylene (0.295 mL, 1.30 mmol) in degassed 1,2-dichloroethane (10 mL) at room temperature. The reaction was heated to 60 ^oC for 2 h, cooled to room temperature and concentrated under reduced pressure to obtain a dark red oil. The residue was dissolved in CH_2Cl_2 and loaded onto a plug of silica, which was initially washed with petroleum ether, followed by Et_2O to elute the intended intermediate (vinyltriethylsilane). After concentration under reduced pressure the residue was dissolved in degassed 1,2-dichloroethane (10 mL) and

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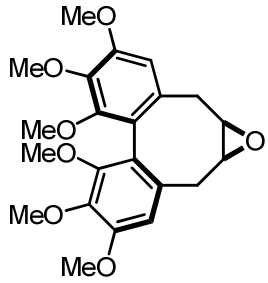
trifluoroacetic acid (1.5 mL) was added at room temperature. The reaction was stirred for 1 h, diluted with water and extracted three times with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure which gave the crude product as a green oil. Further purification by radial chromatography (5:1 petroleum ether : Et_2O) gave the intended alkene **(180)** (0.2434 g, 97 %) as a colorless solid, mp. 184-6 ^oC. IR (KBr) ν_{max} 2995, 2940, 2834, 1594, 1484; ^1H NMR δ 6.52 (s, 2H), 5.80 (m, 2H), 3.90 (s, 6H), 3.89 (s, 6H), 3.68 (s, 6H), 3.00 (m, 4H); ^{13}C NMR 153.3, 150.7, 140.2, 132.9, 129.1, 124.1, 107.6, 61.0, 60.4, 55.9, 33.6; HRMS m/e for $C_{22}H_{26}O_6$ calculated 386.1729 (M^+), found 386.1738.

3,4,5,8,9,10-Hexamethoxy-5H-dibenzo[a,c]cyclooctene oxide (181)



To a stirred solution of freshly prepared dimethyldioxirane[3] (1.40 mL, 0.07 M) in acetone (5 mL) was added alkene **(180)** (0.0320 g, 0.0829 mmol) as a solution in acetone (2 mL). The reaction was monitored by means of TLC, and after complete consumption of the starting material (5 h), the mixture was concentrated under reduced pressure. The crude material was purified by radial chromatography (1:1 petroleum ether : Et_2O) to give the product **(181)** (0.0291 g, 87 %) as a white powder, mp. 195-6 ^oC. IR (KBr) ν_{max} 2935, 2844, 1595, 1459; ^1H NMR δ 6.52 (s, 1H), 6.60 (s, 1H), 3.91 (s, 3H), 3.90 (s, 6H), 3.86 (s, 3H), 3.71 (s, 3H), 3.61 (s, 3H), 3.16 (m, 2H), 3.02 (m, 2H), 2.79 (d, J=14.8, 1H), 2.20 (m, 1H); ^{13}C NMR 153.0, 152.6, 151.9, 151.0, 141.0, 140.6, 133.2, 131.7, 124.7, 122.6, 110.4, 107.3, 61.0, 60.9, 60.6, 60.4, 57.2, 56.0, 55.9, 53.7, 33.8, 32.7; HRMS m/e for $C_{22}H_{26}O_7$ calculated 402.1678 (M^+), found 402.1685.

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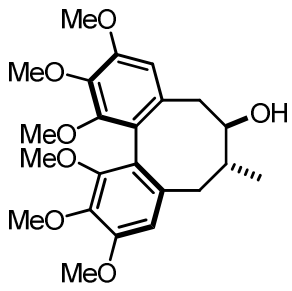
<u>3,4,5,8,9,10-Hexamethoxy-5H-dibenzo[a,c]-2-methylcyclooctanol</u> (182)



MeLi (1.40 mL, 2.24mmol, 1.60 M in hexanes) was added to a stirred suspension of CuI (0.2099 g, 1.10 mmol) in Et_2O (5 mL) at 0 ^oC. After 15 minutes, epoxide **(181)** (0.1108 g, 0.2755 mmol) was added as a solution in toluene (2 mL) and immediately afterwards was added BF_3-OEt_2 (0.052 mL, 0.41 mmol). The reaction mixture was warmed to room temperature, and the progress was monitored by TLC. Upon completion (2 h), the mixture was diluted with a saturated solution of NH_4Cl and extracted three times with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to obtain the crude product. Upon purification with (2 : 1 Et_2O : petroleum ether) the product **(182)** was obtained (0.1059 g, 92 %) as a viscous, colorless oil. IR (KBr) ν_{max} 3509(broad), 2934, 1595, 1458; ^1H NMR δ 6.65 (s, 1H), 6.54 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.89 (s, 6H), 3.72 (t, J=7.5, 1H), 3.60 (s, 6H), 2.72 (m, 1H), 2.55 (m, 2H), 2.39 (m, 1H), 2.10 (t, J=7.5, 1H), 1.79 (d, J=9.4, 1H), 0.83 (d, J=7.4, 3H); ^{13}C NMR 152.3, 152.2, 151.9, 151.5, 140.8, 140.1, 133.4, 130.2, 124.3, 122.9, 110.3, 110.0, 71.1, 61.0, 60.9, 60.6, 60.5, 56.0, 55.9, 37.8, 33.6, 31.9, 17.4; HRMS m/e for $C_{23}H_{30}O_7$ calculated 418.1991 (M^+), found 418.1993.

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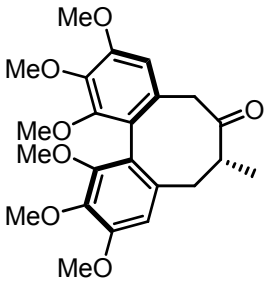
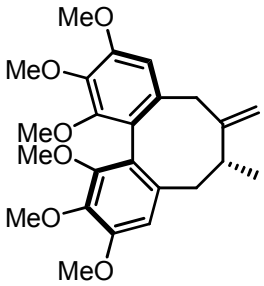
3,4,5,8,9,10-Hexamethoxy-5H-dibenzo[a,c]-2-methylcyclooctanone (183)



To a stirred solution of oxalyl chloride (0.045 mL, 0.51 mmol) in CH_2Cl_2 (5 mL) at -78^oC was added DMSO (0.072 mL, 1.01 mmol); the reaction mixture was stirred for 15 min. To it was added alcohol **(182)** (0.1059 g, 0.25 mmol) as a solution in CH_2Cl_2 (2 mL) and the mixture was stirred at -78 ^oC for 1 h. Subsequently NEt_3 (0.283 ml, 2.02 mmol) was added, and then the reaction mixture was warmed to room temperature. The reaction solution was concentrated under reduced pressure and purified by radial chromatography (1:1 petroleum ether : Et_2O) to afford the desired ketone **(183)** (0.1000 g, 95 %) as a viscous colorless oil. IR (KBr) ν_{max} 2936, 2838, 1700, 1595, 1459; ^1H NMR δ 6.71 (s, 1H), 6.58 (s, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H), 3.68 (s, 3H), 3.67 (s, 3H), 3.54 (d, J=12.0, 1H), 3.11 (d, J=12.0, 1H), 2.82 (dd, J=14.0, 4.0, 1H), 2.69 (m, 1H), 2.48 (dd, J=14.0, 5.2, 1H), 1.16 (d, J=7.3, 3H); ^{13}C NMR 211.1, 153.2, 152.5, 151.7, 151.5, 141.2, 141.1, 131.9, 129.0, 123.6, 123.3, 110.2, 108.0, 61.0, 60.9, 60.7, 60.6, 56.0, 46.0, 45.0, 36.5, 16.6 ; HRMS m/e for $C_{23}H_{28}O_7$ calculated 416.1835 (M^+), found 416.1835.

3,4,5,8,9,10-Hexamethoxy-5H-dibenzo[a,c]-2-methyl-1-methylenecyclooctane (185)



$TiCl_4$ (0.013 mL, 0.12 mmol) was added to a stirred suspension of Mg (0.0120 g, 0.49 mmol) in CH_2Cl_2 (5 mL) at 0 ^oC. Subsequently, ketone **(183)** (0.0254 g, 0.06 mmol) was added as a solution in CH_2Cl_2 (1 mL) and THF (1 mL). The reaction mixture was then stirred at 0 ^oC for 30 min and at room temperature for an additional 20 min. The

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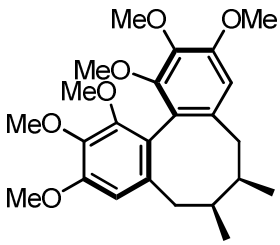
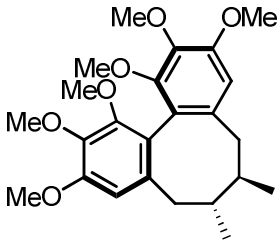
solution was diluted with a saturated solution of K_2CO_3 and extracted three times with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product, which was purified by radial chromatography (3:1 petroleum ether : Et_2O) to give the intended compound **(185)** (0.0194 g, 77 %) as colorless viscous oil. IR (KBr) ν_{max} 3062, 2936, 2835, 1595, 1458; ^{1}H NMR δ 6.68 (s, 1H), 6.58 (s, 1H), 4.89 (d, J=2.0, 1H), 4.76 (d, J=2.0, 1H), 3.93 (s, 9H), 3.89 (s, 3H), 3.65 (s, 3H), 3.63 (s, 3H), 3.03 (d, J=12.0, 1H), 2.96 (d, J=12.0, 1H), 2.73 (m, 1H), 2.57 (m, 2H), 1.05 (d, J=7.3, 3H); ^{13}C NMR 153.9, 152.9, 151.8, 151.5, 151.2, 140.4, 140.3, 136.4, 133.1, 123.6, 122.4, 110.9, 110.3, 106.9, 61.0, 60.9, 60.5, 55.9, 55.8, 38.5, 37.8, 37.1, 20.5.; HRMS m/e for $C_{24}H_{30}O_6$ calculated 414.2042 (M^+), found 414.2035.

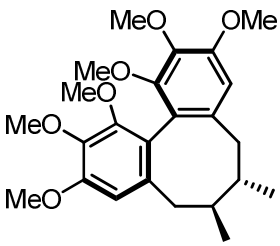
<u>3,4,5,8,9,10-Hexamethoxy-5H-dibenzo[a,c]-1,2-dimethylcyclooctene</u> (186), (187) and (188)



186



187



188

Olefin **(185)** (0.0194 g, 0.0468 mmol) was dissolved in methanol (3 mL), and excess Pd/C (0.2148 g) was added at room temperature. The reaction mixture was placed under an H_2 atmosphere by means of a latex glove balloon. After completion (12 h), the suspension was filtered through a plug of silica by eluting with Et_2O. Further purification with radial

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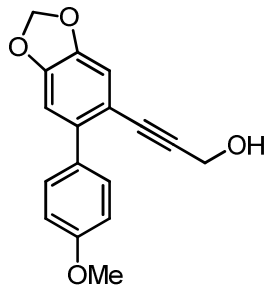
chromatography (3:1 petroleum ether : Et_2O) yielded the intended product as mixture of diastereomers **(186), (187),** and **(188)** (0.0183 g, 93 %) in form of a viscous colorless oil. IR (KBr) ν_{max} 2932, 2871, 1595, 1458; ^{1}H NMR δ 6.57 (s, diastereomer **188**), 6.54 (s, diastereomer **186**), 6.53 (s, diastereomer **186**), 6.52 (s, diastereomer **187**), 3.91 (s), 3.88 (s), 3.87 (s), 3.64 (s), 3.59 (s), 2.62-1.79 (m), 1.05 (d, J=7.2, diastereomer **188**), 1.01 (d, J=7.2, diastereomer **186**), 0.86 (d, J=7.2, diastereomer **187**), 0.74 (d, J=7.2, diastereomer **186**); ^{13}C NMR 152.8, 151.6, 151.5, 151.4, 151.3, 151.1, 140.0, 139.9, 139.7, 139.1, 138.0, 134.1, 133.9, 123.4, 123.3, 122.6, 122.3, 110.4, 110.3, 107.5, 107.1, 61.0, 60.9, 60.5, 55.9, 55.8, 42.7, 40.7, 39.1, 35.8, 35.5, 33.7, 32.9, 23.6, 21.8, 20.3, 12.6 ; HRMS m/e for $C_{24}H_{32}O_6$ calculated 416.2199 (M^+), found 416.2196.

3-(6-(4-Methoxyphenyl)benzo[d][1,3]dioxol-5-yl)prop-2-yn-1-ol (196)



To a stirred solution of CBr_4 (2.2024 g, 6.64 mmol) in CH_2Cl_2 (15 mL) at 0 ^{o}C was added PPh_3 (3.4838 g, 13.28 mmol) in several portions, and the resulting solution was stirred at 0 ^{o}C for 15 min. To reaction mixture was added aldehyde **(194)** (0.6740 g, 2.63 mmol) as a solution in CH_2Cl_2 (2 mL). The reaction was further stirred at 0 ^{o}C for 20 min, and then diluted with water. The extraction was carried out with three portions of CH_2Cl_2, upon which the organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to afford an oily residue. The residue was then dissolved in CH_2Cl_2 and filtered through a plug of silica by eluting with 5:1 petroleum ether : Et_2O. The filtrate was reduced under reduced pressure to obtain the intermediate dibromo alkene (1.1609 g). The intermediate was then dissolved in THF (10 ml) and cooled to -78 ^{o}C, and to this solution

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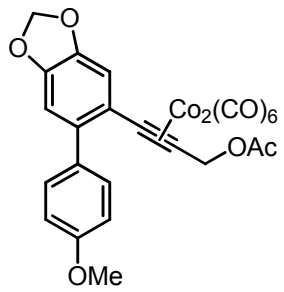
was added *n*-BuLi (1.45 M in hexanes, 4.86 mL, 7.04 mmol) and the mixture was stirred for 0.5 h at -78 ^{o}C. Paraformaldehyde (1.6900 g, 56.3 mmol) was then added as a suspension in THF, and the resulting mixture was allowed to warm up to room temperature and stirred for an additional 2 h. The reaction was then diluted with water and extracted three times with Et_2O, after which the organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to produce the crude material as an oily residue. Purification by column chromatography (3:1 petroleum ether : acetone) produced the intended product **(196)** (0.6409 g, 86 %) as a yellow powder, mp. 130-1 ^{o}C. IR (KBr) ν_{max} 3383, 3002, 2905, 2837, 1481; ^{1}H NMR δ 7.47 (d, J=8.8, 2H), 6.97 (s, 1H), 6.94 (d, J=8.8, 2H), 6.82 (s, 1H), 6.01 (s, 2H), 4.35 (d, J=6.0, 2H), 3.86 (s, 3H), 1.45 (t, J=6.0, 1H); ^{13}C NMR 159.0, 148.3, 146.3, 139.1, 132.7, 130.4, 113.7, 113.4, 112.3, 109.7, 101.5, 88.2, 85.7, 55.3, 51.7; HRMS m/e for $C_{17}H_{14}O_4$ calculated 282.0892 (M^+), found 282.0892.

Hexacarbonyl[μ-η^4(3-(6-(4-methoxyphenyl)benzo[d][1,3]dioxol-5-yl)prop-2-ynyl acetate)]dicobalt (197)



Excess acetic anhydride (1 mL) was added to a stirred solution of alcohol **(196)** (0.6228 g, 2.21 mmol) and excess pyridine (1 mL) in CH_2Cl_2 (5 mL). The reaction progress was monitored by TLC, and when the starting material was consumed (1 h) the reaction mixture was concentrated under reduced pressure. The oily residue was then dissolved in CH_2Cl_2 and an excess of $Co_2(CO)_8$ (ca. 1.5 g) was added at room temperature. The reaction was stirred for 1 h and the solvent was removed under reduced pressure. The solution was filtered through a plug of silica and initially eluted with petroleum ether in order

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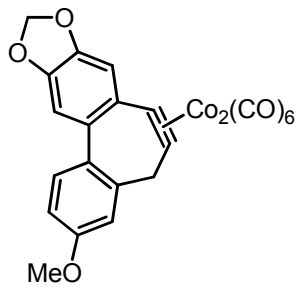
to remove excess $Co_2(CO)_8$. Subsequent elution with Et_2O afforded the crude product. Purification by column chromatography (10:1 petroleum ether : Et_2O) gave the intended product (1.1461 g, 85 %) as a dark red crystals mp. 138-140 ^oC. IR (KBr) ν_{max} 3007, 2961, 2904, 2837, 2089, 2050, 2020, 1477; ^1H NMR δ 7.14 (d, J=8.8, 2H), 7.13 (s, 1H), 7.00 (d, J=8.8, 2H), 6.56 (s, 1H), 6.04 (s, 2H), 4.01 (s, 2H), 3.90 (s, 3H), 2.01 (s, 3H); ^{13}C NMR 199.5, 170.6, 159.6, 147.9, 147.4, 135.5, 134.3, 130.7, 129.1, 114.2, 113.1, 110.4, 101.7, 93.1, 89.3, 64.5, 55.6, 20.4; HRMS m/e for $C_{25}H_{16}Co_2O_{11}$ calculated 581.9407 (M^+-CO), found 581.9410.

Hexacarbonyl[μ-η^4-(3-methoxy-8,9-dioxole-5H-dibenzo[a,c]cycloheptyne)]dicobalt (191)



BF_3-OEt_2 (0.041 mL, 0.33 mmol) was added to a stirred solution of acyclic alkyne complex **(197)** (0.0664 g, 0.11 mmol) and *N,N*-diisopropylethylamine (0.028 mL, 0.16 mmol) in CH_2Cl_2 (25 mL) (4.0×10^{-3} M) at 0 ^oC. The reaction was warmed to room temperature and the reaction progress was monitored by TLC. After consumption of the starting material (6 h) the reaction mixture was diluted with a saturated solution of NH_4Cl and extracted three times with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, which gave the crude product as a dark red oil. Purification by column chromatography (25:1 petroleum ether : Et_2O) afforded the intended product **(191)** (0.0434 g, 72 %) as dark red crystals, mp. 122-3 ^oC. IR (KBr) ν_{max} 3008, 2943, 2901, 2837, 2089, 2052, 2021, 1477; ^1H NMR δ 7.25 (d, J=8.8, 1H), 7.10 (s, 1H), 7.01 (s, 1H), 6.85 (s, 1H), 6.83 (d, J=8.8, 1H), 6.04 (s, 2H), 3.95 (s, 2H), 3.84 (s, 3H); ^{13}C NMR 199.1, 159.0, 147.9, 147.5, 141.4, 134.2, 133.0, 132.8, 130.6, 114.5, 112.3, 111.4,

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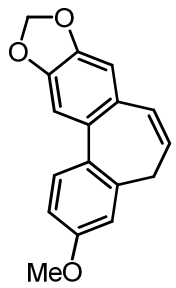
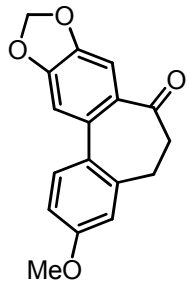
110.1, 103.4, 101.6, 93.4, 55.5, 40.2; HRMS m/e for $C_{23}H_{12}Co_2O_9$ calculated 521.9196 (M^+-CO), found 521.9186.

3-Methoxy-8,9-dioxole-5H-dibenzo[a,c]cycloheptyne (198)



General Procedure I was applied to cobalt complex **(191)** (0.2779 g, 0.50 mmol). Purification by radial chromatography (10:1 petroleum ether : Et_2O) afforded the intended alkene **(198)** (0.1026 g, 76 %) as colorless crystals, mp. 102-4 ^oC. IR (KBr) ν_{max} 3024, 2955, 2837, 1481; ^1H NMR δ 7.39 (d, J=8.5, 1H), 7.11 (s, 1H), 6.85 (dd, J=8.5, 2.7, 1H), 6.77 (s, 1H), 6.76 (d, J=2.7, 1H), 6.45 (d, J=9.9, 1H), 6.10 (m, 1H), 6.02 (s, 2H), 3.85 (s, 3H), 3.12 (s, 1H), 2.88 (s, 1H); ^{13}C NMR 159.4, 146.3, 146.2, 142.7, 134.0, 131.1, 130.6, 130.2, 129.4, 129.1, 111.9, 111.8, 109.0, 108.3, 101.0, 55.3, 33.6; HRMS m/e for $C_{17}H_{14}O_3$ calculated 266.0943 (M^+), found 266.0948.

2,3-Dioxole-9-methoxy-5H-dibenzo[a,c]cyclohepten-5-one (190)



To a solution of alkene **(198)** (0.0981 g, 0.37 mmol) in THF (10 mL) at 0 ^oC was added BH_3-THF (1.86 mL, 1 M solution). The cooling bath was removed and the reaction was stirred at room temperature for 4 h. NaOH (1 mL, 10 % aqueous solution) and H_2O_2 (1 mL, 33 % aqueous solution) were slowly added and the reaction mixture was then heated to 40 ^oC for 2 h. Water was added and reaction mixture was extracted three times with Et_2O. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude

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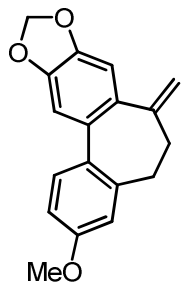
alcohol. The unpurified product was slowly added as a solution in CH_2Cl_2 (1 mL) to a previous mixed oxidant solution prepared from oxalyl chloride (0.062 mL, 0.74 mmol) and DMSO (0.1046 ml, 1.47 mmol) in CH_2Cl_2 (10 mL) at -78 ^oC. NEt_3 (0.41 mL, 2.94 mmol) was added and the resulting mixture was allowed to warm to room temperature. The reaction was quenched with water and extracted three times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude product as a beige powder. Purification by radial chromatography (3:1 petroleum ether : Et_2O) yielded the desired ketone **(190)** (0.0795 g, 76 %) as a colorless powder, mp. 129-131 ^oC. IR (KBr) ν_{max} 3059, 2999, 2837, 1732, 1479; ^1H HMR δ 7.29 (d, J=8.5, 1H), 7.18 (s, 1H), 6.88 (dd, J=8.5, 2.7, 1H), 6.85 (s, 1H), 6.81 (d, J=2.7, 1H), 6.05 (s, 2H), 3.85 (s, 3H), 2.29 (m, 4H); ^{13}C NMR 204.3, 159.4, 151.1, 147.0, 140.9, 135.2, 132.4, 131.2, 131.1, 113.3, 112.6, 109.3, 108.7, 101.8, 55.3, 46.8, 29.8; HRMS m/e for $C_{17}H_{14}O_4$ calculated 282.0892 (M^+), found 282.0892.

2,3-Dioxole-9-methoxy-5H-dibenzo[a,c]-5-methylenecycloheptane (200)



A mixture of potassium *tert*-butoxide (0.3160 g, 2.80 mmol) and methyltriphenylphosphonium bromide (1.0061 g, 2.80 mmol) in toluene (15 mL) were heated to reflux for 2 h. The reaction mixture was cooled to room temperature and ketone **(190)** (0.0795 g, 0.28 mmol) as a solution in toluene (2 mL) was added. The reaction mixture was heated to reflux and the reaction progress was monitored by TLC until completion (1 h). After cooling to room temperature the reaction was diluted with water and extracted three times with Et_2O. The

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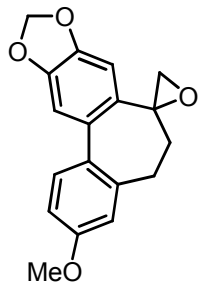
combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude product, which was purified by radial chromatography (30:1 petroleum ether : Et_2O) to afford the intended product **(200)** (0.0547 g, 70 %) as a colorless solid, mp. 172-4 ^oC. IR (KBr) ν_{max} 3079 , 2996, 2832, 1605, 1479; ^1H NMR δ 7.21 (d, J=8.4, 1H), 6.84 (dd, J=8.4, 2.7, 1H), 6.83 (s, 1H), 6.79 (d, J=2.7, 1H), 6.78 (s, 1H), 6.00 (s, 2H), 4.96 (q, J=1.8, 1H), 4.80 (q, J=1.8, 1H), 3.83 (s, 3H), 2.97 (t, J=6.8, 2H), 2.66 (t, J=6.8, 2H); ^{13}C NMR 158.6, 148.5, 147.3, 146.4, 141.0, 135.1, 133.2, 132.7, 129.7, 114.9, 113.8, 111.8, 108.7, 108.5, 101.0, 55.2, 41.9, 31.8; HRMS m/e for $C_{18}H_{16}O_3$ calculated 280.1099 (M^+), found.

2,3-Dioxole-9-methoxy-5H-dibenzo[a,c]-5-oxaspiro[2.6]nonane (201)

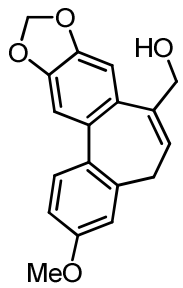


To a stirred solution of freshly prepared dimethyldioxirane[3] (6.50 mL, 0.07 M) in acetone (5 mL) was added alkene **(200)** (0.0861 g, 0.3075 mmol) as a solution in acetone (2 mL). The reaction was monitored by means of TLC, and after complete consumption of the starting material (3 h), the mixture was concentrated under reduced pressure. The crude material was purified by radial chromatography (1:1 petroleum ether : Et_2O) to give the product **(201)** (0.0656 g, 72 %) as a colorless powder, mp. 135-6 ^oC. IR (KBr) ν_{max} 3047 , 2932, 2854, 1607, 1499; ^1H NMR δ 7.23 (d, J=8.3, 1H), 6.96 (s, 1H), 6.87 (dd, J=8.3, 2.6, 1H), 6.84 (s, 1H), 6.83 (d, J=2.6, 1H), 6.00 (s, 2H), 3.85 (s, 3H), 2.66 (m, 2H), 2.62 (d, J=7.8, 1H), 2.56 (m, 1H), 2.36 (s, 1H), 2.09 (m, 1H); ^{13}C NMR 158.9, 147.4, 146.4, 140.8, 133.5, 132.6,

References start on page 109.

131.6, 129.4, 114.4, 111.9, 108.4, 105.9, 101.1, 59.5, 56.7, 55.3, 41.9, 31.1; HRMS m/e for $C_{18}H_{16}O_4$ calculated 296.1049 (M^+), found.

Tenuifolin (189)



To the solution of epoxide **(201)** (0.0275 g, 0.0982 mmol) in THF (3 mL) at room temperature was added ZnI_2 (0.1481 g, 0.4640 mmol). The reaction mixture was stirred for 15 min, and then benzylamine (0.0517 mL, 0.4640 mmol) was added. Reaction progress was monitored by TLC, and upon reaction completion (12 h) solvent was removed under reduced pressure. The crude material was purified by radial chromatography (1 : 1 petroleum ether : Et_2O) to give intended tenuifolin **(189)** (0.0052 g, 19 %) which was spectroscopically identical to the literature report[4].

References start on page 109.

3.2 References

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